(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
16 September 2004 (16.09.2004)

PCT

(10) International Publication Number
WO 2004/078163 A2

(51) International Patent Classification[7]: A61K 9/14, C07C 233/00, C07D 233/00, A61K 31/00

(21) International Application Number: PCT/US2004/006288

(22) International Filing Date: 26 February 2004 (26.02.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/451,213	28 February 2003 (28.02.2003)	US
PCT/US03/06662	3 March 2003 (03.03.2003)	US
60/456,027	18 March 2003 (18.03.2003)	US
60/463,962	18 April 2003 (18.04.2003)	US
10/449,307	30 May 2003 (30.05.2003)	US
PCT/US03/19574	20 June 2003 (20.06.2003)	US
10/601,092	20 June 2003 (20.06.2003)	US
60/487,064	11 July 2003 (11.07.2003)	US
PCT/US03/27772	4 September 2003 (04.09.2003)	US
10/660,202	11 September 2003 (11.09.2003)	US
60/508,208	2 October 2003 (02.10.2003)	US
PCT/US03/41273	24 December 2003 (24.12.2003)	US
60/542,752	6 February 2004 (06.02.2004)	US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PHARMACEUTICAL CO-CRYSTAL COMPOSITIONS

(57) Abstract: A pharmaceutical composition comprising a co-crystal of an API and a co-crystal former; wherein the API has at least one functional group selected from ether, thioether, alcohol, thiol, aldehyde, ketone, thioketone, nitrate ester, phosphate ester, thiophosphate ester, ester, thioester, sulfate ester, carboxylic acid, phosphinic acid, phosphonic acid, sulfonic acid, amide, primary amine, secondary amine, ammonia, tertiary amine, imine, thiocyanate, cyanamide, oxime, nitrile diazo, organohalide, nitro, S-heterocyclic ring, thiophene, N-heterocyclic ring, pyrrole, O-heterocyclic ring, furan, epoxide, peroxide, hydroxamic acid, imidazole, pyridine and the co-crystal former has at least one functional group selected from amine, amide, pyridine, imidazole, indole, pyrrolidine, carbonyl, carboxyl, hydroxyl, phenol, sulfone, sulfonyl, mercapto and methyl thio, such that the API and co-crystal former are capable of co-crystallizing from a solution phase under crystallization conditions.

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PHARMACEUTICAL CO-CRYSTAL COMPOSITIONS

Cross-Reference to Related Applications

This application is a continuation-in-part of United States Patent Application 10/660,202, filed September 11, 2003 (which claims the benefit of US Provisional Patent Application No. 60/451,213 filed on February 28, 2003; U.S. Provisional Patent Application No. 60/463,962, filed on April 18, 2003; and U.S. Provisional Application No. 60/487,064, filed on July 11, 2003 each of which incorporated herein by reference in its entirety for all purposes.

This application is also a continuation-in-part of PCT US03/27772, filed on September 4, 2003 which is a continuation-in-part of U.S. Patent Application No. 10/378,956, filed March 1, 2003, which claims the benefit of U.S. Provisional Application No. 60/360,768, filed March 1, 2002; said PCT US03/27772 also claims the benefit of US Provisional Patent Application No. 60/451,213 filed on February 28, 2003; U.S. Provisional Patent Application No. 60/463,962, filed on April 18, 2003; and U.S. Provisional Application No. 60/487,064, filed on July 11, 2003 each of which are hereby incorporated by reference in its entirety for all purposes.

Said 10/660,202 and PCT US03/27772 are also continuations-in-part of U.S. Patent Application No. 10/637,829, filed August 8, 2003, which is a divisional of U.S. Patent Application No. 10/295,995, filed November 18, 2002, which is a continuation of U.S. Patent Application No.10/232,589, filed September 3, 2002, which claims the benefit of US Provisional Patent Application No. 60/406,974, filed August 30, 2002 and US Provisional Patent Application No.60/380,288, filed May 15, 2002 and US Provisional Patent Application No. 60/356,764, filed February 15, 2002 each of which are hereby incorporated by reference in its entirety for all purposes.

Said 10/660,202 and PCT US03/27772 are also continuations-in-part of US Patent Application No. 10/449,307, filed May 30, 2003 which claims the benefit of US Provisional Patent Application No. 60/463,962 filed April 18, 2003 and US Provisional Patent Application No. 60/444,315, filed January 31, 2003 and US Provisional Patent Application No. 60/439,282 filed January 10, 2003 and US Provisional Patent Application No. 60/384,152, filed May 31, 2002 each of which are hereby incorporated by reference in its entirety for all purposes.

Said 10/660,202 and PCT US03/27772 are also continuations-in-part of US Patent Application No. 10/601,092, filed June 20, 2003, which claims the benefit of US Provisional Patent Application No. 60/451,213, filed February 28, 2003 each of which are hereby incorporated by reference in its entirety for all purposes.

This application is also a continuation-in-part of U.S. Patent Application No. 10/637,829, filed August 8, 2003, which is a divisional of U.S. Patent Application No. 10/295,995, filed

November 18, 2002, which is a continuation of U.S. Patent Application No.10/232,589, filed September 3, 2002, which claims the benefit of US Provisional Patent Application No. 60/406,974, filed August 30, 2002 and US Provisional Patent Application No.60/380,288, filed May 15, 2002 and US Provisional Patent Application No. 60/356,764, filed February 15, 2002 each of which are hereby incorporated by reference in its entirety for all purposes.

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This application is also a continuation-in-part of US Patent Application No. 10/601,092, filed June 20, 2003, which claims the benefit of US Provisional Patent Application No. 60/451,213, filed February 28, 2003 each of which are hereby incorporated by reference in its entirety for all purposes.

This application claims benefit of United States Provisional Patent Application 60/508,208, filed October 2, 2003 and United States Provisional Patent Application 60/542,752, filed February 6, 2004 (Entitled: "Modafinil Compositions"; having Docket TPIP044A+; Magali B. Hickey, Matthew Peterson, Orn Almarsson, and Mark Oliveira) each of which are hereby incorporated by reference in its entirety for all purposes.

This application is also a continuation-in-part of PCT/US03/41273, filed December 24, 2003, which is a continuation in part of PCT/03/19584, filed June 20, 2003, which claims the benefit of U.S. Provisional Application No. 60/390,881, filed on June 21, 2002, U.S. Provisional Application No. 60/426,275, filed on November 14, 2002; U.S. Provisional Application No. 60/427,086 filed on November 15, 2002; U.S. Provisional Application No. 60/429,515 filed on November 26, 2002; U.S. Provisional Application No. 60/437,516 filed on December 30, 2002; and U.S. Provisional Application No. 60/456,027 filed on March 18, 2003 each which are hereby incorporated by reference in its entirety for all purposes.

This application is also a continuation-in-part of United States Patent Application 10/601,092, filed June 20, 2003 which claims the benefit of U.S. Provisional Application No. 60/390,881, filed on June 21, 2002, U.S. Provisional Application No. 60/426,275, filed on November 14, 2002; U.S. Provisional Application No. 60/427,086 filed on November 15, 2002; U.S. Provisional Application No. 60/429,515 filed on November 26, 2002; U.S. Provisional Application No. 60/437,516 filed on December 30, 2002; and U.S. Provisional Application No.

60/456,027 filed on March 18, 2003 each of which are hereby incorporated by reference in its entirety for all purposes.

FIELD OF THE INVENTION

The present invention relates to co-crystal API-containing compositions, pharmaceutical compositions comprising such APIs, and methods for preparing the same.

BACKGROUND OF THE INVENTION

Active pharmaceutical ingredients (API or APIs (plural)) in pharmaceutical compositions can be prepared in a variety of different forms. Such APIs can be prepared so as to have a variety of different chemical forms including chemical derivatives or salts. Such APIs can also be prepared to have different physical forms. For example, the APIs may be amorphous, may have different crystalline polymorphs, or may exist in different solvation or hydration states. By varying the form of an API, it is possible to vary the physical properties thereof. For example, crystalline polymorphs typically have different solubilities from one another, such that a more thermodynamically stable polymorph is less soluble than a less thermodynamically stable polymorph. Pharmaceutical polymorphs can also differ in properties such as shelf-life, bioavailability, morphology, vapour pressure, density, colour, and compressibility. Accordingly, variation of the crystalline state of an API is one of many ways in which to modulate the physical properties thereof.

It would be advantageous to have new forms of these APIs that have improved properties, in particular, as oral formulations. Specifically, it is desirable to identify improved forms of APIs that exhibit significantly improved properties including increased aqueous solubility and stability. Further, it is desirable to improve the processability, or preparation of pharmaceutical formulations. For example, needle-like crystal forms or habits of APIs can cause aggregation, even in compositions where the API is mixed with other substances, such that a non-uniform mixture is obtained. It is also desirable to increase or decrease the dissolution rate of API-containing pharmaceutical compositions in water, increase or decrease the bioavailability of orally-administered compositions, and provide a more rapid or more delayed onset to therapeutic effect. It is also desirable to have a form of the API which, when administered to a subject, reaches a peak plasma level faster or slower, has a longer lasting therapeutic plasma concentration, and higher or lower overall exposure when compared to equivalent amounts of the API in its presently-known form. The improved properties discussed above can be altered in a way which is most beneficial to a specific API for a specific therapeutic effect.

SUMMARY OF THE INVENTION

It has now been found that new co-crystalline forms of APIs can be obtained which improve the properties of APIs as compared to such APIs in a non-co-crystalline state (free acid, free base, zwitter ions, salts, etc.).

Accordingly, in a first aspect, the present invention provides a co-crystal pharmaceutical composition comprising an API compound and a co-crystal former, such that the API and co-crystal former are capable of co-crystallizing from a solid or solution phase under crystallization conditions.

Another aspect of the present invention provides a process for the production of a pharmaceutical composition, which process comprises:

(1) providing an API which has at least one functional group selected from ether, thioether, alcohol, thiol, aldehyde, ketone, thioketone, nitrate ester, phosphate ester, thiophosphate ester, ester, thioester, sulfate ester, carboxylic acid, phosphonic acid, phosphinic acid, sulfonic acid, amide, primary amine, secondary amine, ammonia, tertiary amine, imine, thiocyanate, cyanamide, oxime, nitrile, diazo, organohalide, nitro, S-heterocyclic ring, thiophene, N-heterocyclic ring, pyrrole, O-heterocyclic ring, furan, epoxide, peroxide, hydroxamic acid, imidazole, and pyridine;

(2) providing a co-crystal former which has at least one functional group selected from ether, thioether, alcohol, thiol, aldehyde, ketone, thioketone, nitrate ester, phosphate ester, thiophosphate ester, ester, thioester, sulfate ester, carboxylic acid, phosphonic acid, phosphinic acid, sulfonic acid, amide, primary amine, secondary amine, ammonia, tertiary amine, imine, thiocyanate, cyanamide, oxime, nitrile, diazo, organohalide, nitro, S-heterocyclic ring, thiophene, N-heterocyclic ring, pyrrole, O-heterocyclic ring, furan, epoxide, peroxide, hydroxamic acid, imidazole, and pyridine;

(3) grinding, heating, co-subliming, co-melting, or contacting in solution the API with the co-crystal former under crystallization conditions;

(4) isolating co-crystals formed thereby; and

(5) incorporating the co-crystals into a pharmaceutical composition.

A further aspect of the present invention provides a process for the production of a pharmaceutical composition, which comprises:

(1) grinding, heating, co-subliming, co-melting, or contacting in solution an API compound with a co-crystal former, under crystallization conditions, so as to form a solid phase;

(2) isolating co-crystals comprising the API and the co-crystal former; and

(3) incorporating the co-crystals into a pharmaceutical composition.

In a further aspect, the present invention provides a process for the production of a pharmaceutical composition, which comprises:

(1) providing (*i*) an API or a plurality of different APIs, and (*ii*) a co-crystal former or a plurality of different co-crystal formers, wherein at least one of the APIs and the co-crystal formers is provided as a plurality thereof;

(2) isolating co-crystals comprising the API and the co-crystal former; and

(3) incorporating the co-crystals into a pharmaceutical composition.

Solubility Modulation

In a further aspect, the present invention provides a process for modulating the solubility of an API, which process comprises:

(1) grinding, heating, co-subliming, co-melting, or contacting in solution the API with a co-crystal former under crystallization conditions, so as to form a co-crystal of the API and the co-crystal former; and

(2) isolating co-crystals comprising the API and the co-crystal former.

Dissolution Modulation

In a further aspect, the present invention provides a process for modulating the dissolution of an API, whereby the aqueous dissolution rate or the dissolution rate in simulated gastric fluid or in simulated intestinal fluid, or in a solvent or plurality of solvents is increased or decreased, which process comprises:

(1) grinding, heating, co-subliming, co-melting, or contacting in solution the API with a co-crystal former under crystallization conditions, so as to form a co-crystal of the API and the co-crystal former; and

(2) isolating co-crystals comprising the API and the co-crystal former.

In one embodiment, the dissolution of the API is increased.

Bioavailability Modulation

In a further aspect, the present invention provides a process for modulating the bioavailability of an API, whereby the AUC is increased, the time to T_{max} is reduced, the length of time the concentration of the API is above ½ T_{max} is increased, or C_{max} is increased, which process comprises:

(1) grinding, heating, co-subliming, co-melting, or contacting in solution the API with a co-crystal former under crystallization conditions, so as to form a co-crystal of the API and the co-crystal former; and

(2) isolating co-crystals comprising the API and the co-crystal former.

Dose Response Modulation

In a further aspect the present invention provides a process for improving the linearity of a dose response of an API, which process comprises:

(1) grinding, heating, co-subliming, co-melting, or contacting in solution an API with a co-crystal former under crystallization conditions, so as to form a co-crystal of the API and the co-crystal former; and

(2) isolating co-crystals comprising the API and the co-crystal former.

Increased Stability

In a still further aspect the present invention provides a process for improving the stability of a pharmaceutical salt, which process comprises:

(1) grinding, heating, co-subliming, co-melting, or contacting in solution the pharmaceutical salt with a co-crystal former under crystallization conditions, so as to form a co-crystal of the API and the co-crystal former; and

(2) isolating co-crystals comprising the API and the co-crystal former.

Difficult to Salt or Unsaltable Compounds

In a still further aspect the present invention provides a process for making co-crystals of difficult to salt or unsaltable APIs, which process comprises:

(1) grinding, heating, co-subliming, co-melting, or contacting in solution the API with a co-crystal former under crystallization conditions, so as to form a co-crystal of the API and the co-crystal former; and

(2) isolating co-crystals comprising the API and the co-crystal former.

Decreasing Hygroscopicity

In a still further aspect the present invention provides a method for decreasing the hygroscopicity of an API, which method comprises:

(1) grinding, heating, co-subliming, co-melting, or contacting in solution the API with a co-crystal former under crystallization conditions, so as to form a co-crystal of the API and the co-crystal former; and

(2) isolating co-crystals comprising the API and the co-crystal former.

Crystallizing Amorphous Compounds

In a still further embodiment aspect the present invention provides a process for crystallizing an amorphous compound, which process comprises:

(1) grinding, heating, co-subliming, co-melting, or contacting in solution the API with a co-crystal former under crystallization conditions, so as to form a co-crystal of the API and the co-crystal former; and

(2) isolating co-crystals comprising the API and the co-crystal former.

Decreasing Form Diversity

In a still further embodiment aspect the present invention provides a process for reducing the form diversity of an API, which process comprises:

(1) grinding, heating, co-subliming, co-melting, or contacting in solution the API with a co-crystal former under crystallization conditions, so as to form a co-crystal of the API and the co-crystal former; and

(2) isolating co-crystals comprising the API and the co-crystal former.

Morphology Modulation

In a still further embodiment aspect the present invention provides a process for modifying the morphology of an API, which process comprises:

(1) grinding, heating, co-subliming, co-melting, or contacting in solution the API with a co-crystal former under crystallization conditions, so as to form a co-crystal of the API and the co-crystal former; and

(2) isolating co-crystals comprising the API and the co-crystal former.

In a further aspect, the present invention provides a co-crystal composition comprising a co-crystal, wherein said co-crystal comprises an API compound and a co-crystal former. In further embodiments the co-crystal has an improved property as compared to the free form (including a free acid, free base, zwitter ion, hydrate, solvate, etc.) or a salt (which includes salt hydrates and solvates). In further embodiments, the improved property is selected from the group consisting of: increased solubility, increased dissolution, increased bioavailability, increased dose

response, decreased hygroscopicity, a crystalline form of a normally amorphous compound, a crystalline form of a difficult to salt or unsaltable compound, decreased form diversity, more desired morphology, or other property described herein.

BRIEF DESCRIPTION OF THE DRAWINGS

Figs. 1A-B PXRD diffractograms of a co-crystal comprising celecoxib and nicotinamide, with the background removed and as collected, respectively.

Fig. 2 DSC thermogram for a co-crystal comprising celecoxib and nicotinamide.

Fig. 3 TGA thermogram for a co-crystal comprising celecoxib and nicotinamide.

Fig. 4 Raman spectrum for a co-crystal comprising celecoxib and nicotinamide.

Figs. 5A-B PXRD diffractograms of a co-crystal comprising celecoxib and 18-crown-6, with the background removed and as collected, respectively.

Fig. 6 DSC thermogram for a co-crystal comprising celecoxib and 18-crown-6.

Fig. 7 TGA thermogram for a co-crystal comprising celecoxib and 18-crown-6.

Figs. 8A-B PXRD diffractograms of a co-crystal comprising topiramate and 18-crown-6, with the background removed and as collected, respectively.

Fig. 9 DSC thermogram for a co-crystal comprising topiramate and 18-crown-6.

Figs. 10A-B PXRD diffractograms of a co-crystal comprising olanzapine and nicotinamide (Form I), with the background removed and as collected, respectively.

Fig. 11 DSC thermogram for a co-crystal comprising olanzapine and nicotinamide (Form I).

Fig. 12 PXRD diffractogram of a co-crystal comprising olanzapine and nicotinamide (Form II).

Figs. 13A-B PXRD diffractograms of a co-crystal comprising olanzapine and nicotinamide (Form III), with the background removed and as collected, respectively.

Figs. 14A-D Packing diagrams and crystal structure of a co-crystal comprising olanzapine and nicotinamide (Form III).

Fig. 15 PXRD diffractogram of a co-crystal comprising *cis*-itraconazole and succinic acid.

Fig. 16 DSC thermogram for a co-crystal comprising *cis*-itraconazole and succinic acid.

Fig. 17 PXRD diffractogram of a co-crystal comprising *cis*-itraconazole and fumaric acid.

Fig. 18 DSC thermogram for a co-crystal comprising *cis*-itraconazole and fumaric acid.

Fig. 19 PXRD diffractogram of a co-crystal comprising *cis*-itraconazole and L-tartaric acid.

Fig. 20 DSC thermogram for a co-crystal comprising *cis*-itraconazole and L-tartaric acid.

Fig. 21 PXRD diffractogram of a co-crystal comprising *cis*-itraconazole and L-malic acid.

Fig. 22 DSC thermogram for a co-crystal comprising *cis*-itraconazole and L-malic acid.

Fig. 23 PXRD diffractogram of a co-crystal comprising *cis*-itraconazoleHCl and DL-tartaric acid.

Fig. 24 DSC thermogram for a co-crystal comprising *cis*-itraconazoleHCl and DL-tartaric acid.
Fig. 25 PXRD diffractogram of a co-crystal comprising modafinil and malonic acid (Form I).
Fig. 26 DSC thermogram for a co-crystal comprising modafinil and malonic acid (Form I).
Fig. 27 Raman spectrum for a co-crystal comprising modafinil and malonic acid (Form I).
Fig. 28 PXRD diffractogram of a co-crystal comprising modafinil and malonic acid (Form II).
Figs. 29A-B PXRD diffractograms of a co-crystal comprising modafinil and glycolic acid, with the background removed and as collected, respectively.
Figs. 30A-B PXRD diffractograms of a co-crystal comprising modafinil and maleic acid, with the background removed and as collected, respectively.
Figs. 31A-B PXRD diffractograms of a co-crystal comprising 5-fluorouracil and urea, with the background removed and as collected, respectively.
Fig. 32 DSC thermogram for a co-crystal comprising 5-fluorouracil and urea.
Fig. 33 TGA thermogram for a co-crystal comprising 5-fluorouracil and urea.
Fig. 34 Raman spectrum for a co-crystal comprising 5-fluorouracil and urea.
Figs. 35A-B PXRD diffractograms of a co-crystal comprising hydrochlorothiazide and nicotinic acid, with the background removed and as collected, respectively.
Figs. 36A-B PXRD diffractograms of a co-crystal comprising hydrochlorothiazide and 18-crown-6, with the background removed and as collected, respectively.
Figs. 37A-B PXRD diffractograms of a co-crystal comprising hydrochlorothiazide and piperazine, with the background removed and as collected, respectively.
Figs. 38A-B An acetaminophen 1-D polymeric chain and a co-crystal of acetaminophen and 4,4'-bipyridine, respectively.
Figs. 39A-B Pure phenytoin and a co-crystal with phenytoin and pyridone, respectively.
Figs. 40A-D Pure aspirin and the corresponding crystal structure are shown in Figures 40A and 40B, respectively. Figures 40C and 40D show the supramolecular entity containing the synthon and corresponding co-crystal of aspirin and 4,4'-bipyridine, respectively.

Figs. 41A-D Pure ibuprofen and the corresponding crystal structure are shown in Figures 41A and 41B, respectively. Figures 41C and 41D show the supramolecular entity containing the synthon and corresponding co-crystal of ibuprofen and 4,4'-bipyridine, respectively.
Figs. 42A-D Pure flurbiprofen and the corresponding crystal structure are shown in Figures 42A and 42B, respectively. Figures 42C and 42D show the supramolecular synthon and corresponding co-crystal of flurbiprofen and 4,4'-bipyridine, respectively.
Figs. 43A-B The supramolecular entity containing the synthon and the corresponding co-crystal

structure of flurbiprofen and trans-1,2-bis(4-pyridyl)ethylene, respectively.

Figs. 44A–B The crystal structure of pure carbamazepine and the co-crystal structure of carbamazepine and *p*-phthalaldehyde, respectively.

Fig. 45 A packing diagram of the co-crystal structure of carbamazepine and nicotinamide.

Fig. 46 PXRD diffractogram of a co-crystal comprising carbamazepine and nicotinamide.

Fig. 47 DSC thermogram for a co-crystal comprising carbamazepine and nicotinamide.

Fig. 48 A packing diagram of the co-crystal structure of carbamazepine and saccharin.

Fig. 49 PXRD diffractogram of a co-crystal comprising carbamazepine and saccharin.

Fig. 50 DSC thermogram for a co-crystal comprising carbamazepine and saccharin.

Figs. 51A-B The crystal structure of carbamazepine and the co-crystal structure of carbamazepine and 2,6-pyridinedicarboxylic acid, respectively.

Figs. 52A-B The crystal structure of carbamazepine and the co-crystal structure of carbamazepine and 5-nitroisophthalic acid, respectively.

Figs. 53A-B The crystal structure of carbamazepine and the co-crystal structure of carbamazepine and 1,3,5,7-adamantanetetracarboxylic acid, respectively.

Figs. 54A-B The crystal structure of carbamazepine and the co-crystal structure of carbamazepine and benzoquinone, respectively.

Figs. 55A-B The crystal structure of carbamazepine and the co-crystal structure of carbamazepine and trimesic acid, respectively.

Fig. 56 PXRD diffractogram of a co-crystal comprising carbamazepine and trimesic acid.

Fig. 57 Dissolution profile for a co-crystal of celecoxib:nicotinamide vs. celecoxib free acid.

Fig. 58 Dissolution profile for co-crystals of itraconazole:succinic acid, itraconazle:tartaric acid and itraconazole:malic acid vs. itraconazole free base.

Fig. 59 Hygroscopicity profile for a co-crystal of celecoxib:nicotinamide vs. celecoxib sodium.

Fig. 60 Hydrogen-bonding motifs observed in co-crystals.

Fig. 61 Dissolution profile of several formulations of modafinil free form and modafinil:malonic acid (Form I).

DETAILED DESCRIPTION OF THE INVENTION

The term "co-crystal" as used herein means a crystalline material comprised of two or more unique solids at room temperature, each containing distinctive physical characteristics, such as structure, melting point and heats of fusion, with the exception that, if specifically stated, the API may be a liquid at room temperature. The co-crystals

of the present invention comprise a co-crystal former H-bonded to an API. The co-crystal former may be H-bonded directly to the API or may be H-bonded to an additional molecule which is bound to the API. The additional molecule may be H-bonded to the API or bound ionically or covalently to the API. The additional molecule could also be a different API. Solvates of API compounds that do not further comprise a co-crystal former are not co-crystals according to the present invention. The co-crystals may however, include one or more solvate molecules in the crystalline lattice. That is, solvates of co-crystals, or a co-crystal further comprising a solvent or compound that is a liquid at room temperature, is included in the present invention, but crystalline material comprised of only one solid and one or more liquids (at room temperature) are not included in the present invention, with the previously noted exception of specifically stated liquid APIs. The co-crystals may also be a co-crystal between a co-crystal former and a salt of an API, but the API and the co-crystal former of the present invention are constructed or bonded together through hydrogen bonds. Other modes of molecular recognition may also be present including, pi-stacking, guest-host complexation and van der Waals interactions. Of the interactions listed above, hydrogen-bonding is the dominant interaction in the formation of the co-crystal, (and a required interaction according to the present invention) whereby a non-covalent bond is formed between a hydrogen bond donor of one of the moieties and a hydrogen bond acceptor of the other. Hydrogen bonding can result in several different intermolecular configurations. For example, hydrogen bonds can result in the formation of dimers, linear chains, or cyclic structures. These configurations can further include extended (two-dimensional) hydrogen bond networks and isolated triads (Fig. 60). An alternative embodiment provides for a co-crystal wherein the co-crystal former is a second API. In another embodiment, the co-crystal former is not an API. In another embodiment the co-crystal comprises two co-crystal formers. For purposes of the present invention, the chemical and physical properties of an API in the form of a co-crystal may be compared to a reference compound that is the same API in a different form. The reference compound may be specified as a free form, or more specifically, a free acid, free base, or zwitterion; a salt, or more specifically for example, an inorganic base addition salt such as sodium, potassium, lithium, calcium, magnesium, ammonium, aluminum salts or organic base

addition salts, or an inorganic acid addition salts such as HBr, HCl, sulfuric, nitric, or phosphoric acid addition salts or an organic acid addition salt such as acetic, propionic, pyruvic, malanic, succinic, malic, maleic, fumaric, tartaric, citric, benzoic, methanesulfonic, ethanesulforic, stearic or lactic acid addition salt; an anhydrate or hydrate of a free form or salt, or more specifically, for example, a hemihydrate, monohydrate, dihydrate, trihydrate, quadrahydrate, pentahydrate, sesquihydrate; or a solvate of a free form or salt. For example, the reference compound for an API in salt form co-crystallized with a co-crystal former can be the API salt form. Similarly, the reference compound for a free acid API co-crystallized with a co-crystal former can be the free acid API. The reference compound may also be specified as crystalline or amorphous.

According to the present invention, the co-crystals can include an acid addition salt or base addition salt of an API. Acid addition salts include, but are not limited to, inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, and phosphoric acid, and organic acids such as acetic acid, propionic acid, hexanoic acid, heptanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartatic acid, citric acid, benzoic acid, o-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, madelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, *p*-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, *p*-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutaric acid, hydroxynaphthoic acid, salicylic acid, stearic acid, and muconic acid. Base addition salts include, but are not limited to, inorganic bases such as sodium, potassium, lithium, ammonium, calcium and magnesium salts, and organic bases such as primary, secondary and tertiary amines (e.g. isopropylamine, trimethyl amine, diethyl amine, tri(iso-propyl) amine, tri(n-propyl) amine, ethanolamine, 2-dimethylaminoethanol, tromethamine, lysine, arginine, histidine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, N-alkylglucamines, theobromine, purines, piperazine, piperidine,

morpholine, and N-ethylpiperidine).

The ratio of API to co-crystal former may be stoichiometric or non-stoichiometric according to the present invention. For example, 1:1, 1.5:1, 1:1.5, 2:1 and 1:2 ratios of API:co-crystal former are acceptable.

It has surprisingly been found that when an API and a selected co-crystal former are allowed to form co-crystals, the resulting co-crystals give rise to improved properties of the API, as compared to the API in a free form (including free acids, free bases, and zwitterions, hydrates, solvates, etc.), or an acid or base salt thereof particularly with respect to: solubility, dissolution, bioavailability, stability, Cmax, Tmax, processability, longer lasting therapeutic plasma concentration, hygroscopicity, crystallization of amorphous compounds, decrease in form diversity (including polymorphism and crystal habit), change in morphology or crystal habit, etc. For example, a co-crystal form of an API is particularly advantageous where the original API is insoluble or sparingly soluble in water. Additionally, the co-crystal properties conferred upon the API are also useful because the bioavailability of the API can be improved and the plasma concentration and/or serum concentration of the API can be improved. This is particularly advantageous for orally-administrable formulations. Moreover, the dose response of the API can be improved, for example by increasing the maximum attainable response and/or increasing the potency of the API by increasing the biological activity per dosing equivalent.

Accordingly, in a first aspect, the present invention provides a pharmaceutical composition comprising a co-crystal of an API and a co-crystal former, such that the API and co-crystal former are capable of co-crystallizing from a solution phase under crystallization conditions or from the solid-state, for example, through grinding, heating, or through vapor transfer (e.g., co-sublimation). In another aspect, the API has at least one functional group selected from ether, thioether, alcohol, thiol, aldehyde, ketone, thioketone, nitrate ester, phosphate ester, thiophosphate ester, ester, thioester, sulfate ester, carboxylic acid, phosphonic acid, phosphinic acid, sulfonic acid, amide, primary amine, secondary amine, ammonia, tertiary amine, imine, thiocyanate, cyanamide, oxime, nitrile, diazo, organohalide, nitro, S-heterocyclic ring, thiophene, N-heterocyclic ring, pyrrole, O-heterocyclic ring, furan, epoxide, peroxide, hydroxamic acid, imidazole, and

pyridine and a co-crystal former which has at least one functional group selected from ether, thioether, alcohol, thiol, aldehyde, ketone, thioketone, nitrate ester, phosphate ester, thiophosphate ester, ester, thioester, sulfate ester, carboxylic acid, phosphonic acid, phosphinic acid, sulfonic acid, amide, primary amine, secondary amine, ammonia, tertiary amine, imine, thiocyanate, cyanamide, oxime, nitrile, diazo, organohalide, nitro, S-heterocyclic ring, thiophene, N-heterocyclic ring, pyrrole, O-heterocyclic ring, furan, epoxide, peroxide, hydroxamic acid, imidazole, and pyridine, or a functional group in a Table herein, such that the API and co-crystal former are capable of co-crystallizing from a solution phase under crystallization conditions.

The co-crystals of the present invention are formed where the API and co-crystal former are bonded together through hydrogen bonds. Other non-covalent interactions, including pi-stacking and van der Waals interactions, may also be present.

In one embodiment, the co-crystal former is selected from the co-crystal formers of Table I and Table II. In other embodiments, the co-crystal former of Table I is specified as a Class 1, Class 2, or Class 3 co-crystal former (see column labeled "class" Table I). In another embodiment, the difference in pK_a value of the co-crystal former and the API is less than 2. In other embodiments, the difference in pK_a values of the co-crystal former and API is less than 3, less than 4, less than 5, between 2 and 3, between 3 and 4, or between 4 and 5. Table I lists multiple pK_a values for co-crystal formers having multiple functionalities. It is readily apparent to one skilled in the art the particular functional group corresponding to a particular pK_a value.

In another embodiment the particular functional group of a co-crystal former interacting with the API is specified (see for example Table I, columns labeled "Functionality" and "Molecular Structure" and the column of Table II labeled "Co-Crystal Former Functional Group"). In a further embodiment the functional group of the API interacting with the co-crystal former functional group is specified (see, for example, Tables II and III).

In another embodiment, the co-crystal comprises more than one co-crystal former. For example, two, three, four, five, or more co-crystal formers can be incorporated in a co-crystal with an API. Co-crystals which comprise two or more co-crystal formers and an API are bound together via hydrogen bonds. In one embodiment, incorporated co-

crystal formers are hydrogen bonded to the API molecules. In another embodiment, co-crystal formers are hydrogen bonded to either the API molecules or the incorporated co-crystal formers.

In a further embodiment, several co-crystal formers can be contained in a single compartment, or kit, for ease in screening an API for potential co-crystal species. The co-crystal kit can comprise 5, 10, 15, 20, 25, 30, 40, 50, 60, 70, 80, 90, 100, or more of the co-crystal formers in Tables I and II. The co-crystal formers are in solid form or in solution and in an array of individual reaction vials such that individual co-crystal formers can be tested with one or more APIs by one or more crystallization methods or multiple co-crystal formers can be easily tested against one or more compounds by one or more crystallization methods. The crystallization methods include, but are not limited to, melt recrystallization, grinding, milling, standing, co-crystal formation from solution by evaporation, thermally driven crystallization from solution, co-crystal formation from solution by addition of anti-solvent, co-crystal formation from solution by vapor-diffusion, co-crystal formation from solution by drown-out, co-crystal formation from solution by any combination of the above mentioned techniques, co-crystal formation by co-sublimation, co-crystal formation by sublimation using a Knudsen cell apparatus, co-crystal formation by standing the desired components of the co-crystal in the presence of solvent vapor, co-crystal formation by slurry conversion of the desired components of the co-crystal in a solvent or mixtures of solvents, or co-crystal formation by any combination of the above techniques in the presence of additives, nucleates, crystallization enhancers, precipitants, chemical stabilizers, or anti-oxidants. The co-crystallization kits can be used alone or as part of larger crystallization experiments. For example, kits can be constructed as single co-crystal former single well kits, single co-crystal former multi-well kits, multi-co-crystal former single well kits, or multi-co-crystal former multi-well kits. High-throughput crystallization (e.g., the CrystalMax™ platform) can be used to construct and customize co-crystal former kits. Multi-well plates (e.g., 96 wells, 384 wells, 1536 wells, etc.), for example, can be used to store or employ an array of co-crystal formers.

In a further embodiment, the API is selected from an API of Table IV or elsewhere herein. For pharmaceuticals listed in Table IV, co-crystals can comprise such

APIs in free form (i.e. free acid, free base, zwitter ion), salts, solvates, hydrates, or the like. For APIs in Table IV listed as salts, solvates, hydrates, and the like, the API can either be of the form listed in Table IV or its corresponding free form, or of another form that is not listed. Table IV includes the CAS number, chemical name, or a PCT or patent reference (each incorporated herein in their entireties). In further embodiments, the functional group of the particular API interacting with the co-crystal former is specified. A specific functional group of a co-crystal former, a specific co-crystal former, or a specified functional group or a specific co-crystal former interacting with the particular API may also be specified. It is noted that for Table II, the co-crystal former, and optionally the specific functionality, and each of the listed corresponding interacting groups are included as individual species of the present invention. Thus, each specific combination of a co-crystal former and one of the interacting groups in the same row may be specified as a species of the present invention. The same is true for other combinations as discussed in the Tables and elsewhere herein.

In another embodiment of the present invention, the co-crystal comprises an API wherein the API forms a dimeric primary amide structure via hydrogen bonds with an R^2_2 (8) motif. In such a structure, the NH_2 moiety can also participate in a hydrogen bond with a donor or an acceptor moiety from, for example, a co-crystal former or an additional (third) molecule, and the C=O moiety can participate in a hydrogen bond with a donor moiety from the co-crystal former or the additional molecule. In a further embodiment, the dimeric primary amide structure further comprises one, two, three, or four hydrogen bond donors. In a further embodiment, the dimeric primary amide structure further comprises one or two hydrogen bond acceptors. In a further embodiment, the dimeric primary amide structure further comprises a combination of hydrogen bond donors and acceptors. For example, the dimeric primary amide structure can further comprise one hydrogen bond donor and one hydrogen bond acceptor, one hydrogen bond donor and two hydrogen bond acceptors, two hydrogen bond donors and one hydrogen bond acceptor, two hydrogen bond donors and two hydrogen bond acceptors, or three hydrogen bond donors and one hydrogen bond acceptor. Two non-limiting examples of APIs which form a dimeric primary amide co-crystal structure include modafinil and carbamazepine. Some examples of APIs which include a primary

amide functional group include, but are not limited to, arotinolol, atenolol, carpipramine, cefotetan, cefsulodin, docapromine, darifenacin, exalamide, fidarestat, frovatriptan, silodosin, levetiracetam, MEN-10700, mizoribine, oxiracetam, piracetam, protirelin, TRH, ribavirin, valrecemide, temozolomide, tiazofurin, antiPARP-2, levovirin, N-benzyloxycarbonyl glycinamide, and UCB-34714.

In each process according to the invention, there is a need to contact the API with the co-crystal former. This may involve grinding or milling the two solids together or melting one or both components and allowing them to recrystallize. The use of a granulating liquid may improve or may impede co-crystal formation. Non-limiting examples of tools useful for the formation of co-crystals may include, for example, an extruder or a mortar and pestle. Further, contacting the API with the co-crystal former may also involve either solubilizing the API and adding the co-crystal former, or solubilizing the co-crystal former and adding the API. Crystallization conditions are applied to the API and co-crystal former. This may entail altering a property of the solution, such as pH or temperature and may require concentration of the solute, usually by removal of the solvent, typically by drying the solution. Solvent removal results in the concentration of both API and co-crystal former increasing over time so as to facilitate crystallization. For example, evaporation, cooling, co-sublimation, or the addition of an antisolvent may be used to crystallize co-crystals. In another embodiment, a slurry comprising an API and a co-crystal former is used to form co-crystals. Once the solid phase comprising any crystals is formed, this may be tested as described herein.

The manufacture of co-crystals on a large and/or commercial scale may be successfully completed using one or more of the processes and techniques described herein. For example, crystallization of co-crystals from a solvent and grinding or milling are conceivable non-limiting processes.

In another embodiment, the use of an excess (more than 1 molar equivalent for a 1:1 co-crystal) of a co-crystal former has been shown to drive the formation of stoichiometric co-crystals. For example, co-crystals with stoichiometries of 1:1, 2:1, or 1:2 can be produced by adding co-crystal former in an amount that is 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 50, 75, 100 times or more than the stoichiometric amount for a given co-crystal. Such an excessive use of a co-crystal former to form a co-crystal can be

employed in solution or when grinding an API and a co-crystal former to drive co-crystal formation.

In another embodiment, the present invention provides for the use of an ionic liquid as a medium for the formation of a co-crystal, and can also be used to crystallize other forms in addition to co-crystals (e.g., salts, solvates, free acid, free base, zwitterions, etc.). This medium is useful, for example, where the above methods do not work or are difficult or impossible to control. Several non-limiting examples of ionic liquids useful in co-crystal formation are: 1-butyl-3-methylimidazolium lactate, 1-ethyl-3-methylimidazolium lactate, and 1-butylpyridinium hexafluorophosphate.
The co-crystals obtained as a result of one or more of the above processes or techniques may be readily incorporated into a pharmaceutical composition by conventional means. Pharmaceutical compositions in general are discussed in further detail below and may further comprise a pharmaceutically-acceptable diluent, excipient or carrier.

In a further aspect, the present invention provides a process for the production of a pharmaceutical composition, which process comprises:

(1) providing an API which has at least one functional group selected from ether, thioether, alcohol, thiol, aldehyde, ketone, thioketone, nitrate ester, phosphate ester, thiophosphate ester, ester, thioester, sulfate ester, carboxylic acid, phosphonic acid, phosphinic acid, sulfonic acid, amide, primary amine, secondary amine, ammonia, tertiary amine, imine, thiocyanate, cyanamide, oxime, nitrile diazo, organohalide, nitro, S-heterocyclic ring, thiophene, N-heterocyclic ring, pyrrole, O-heterocyclic ring, furan, epoxide, peroxide, hydroxamic acid, imidazole, and pyridine or of Table II or III;

(2) providing a co-crystal former which has at least one functional group selected from ether, thioether, alcohol, thiol, aldehyde, ketone, thioketone, nitrate ester, phosphate ester, thiophosphate ester, ester, thioester, sulfate ester, carboxylic acid, phosphonic acid, phosphinic acid, sulfonic acid, amide, primary amine, secondary amine, ammonia, tertiary amine, imine, thiocyanate, cyanamide, oxime, nitrile, diazo, organohalide, nitro, S-heterocyclic ring, thiophene, N-heterocyclic ring, pyrrole, O-heterocyclic ring, furan, epoxide, peroxide, hydroxamic acid, imidazole, and pyridine or of Table I, II, or III;

(3) grinding, heating or contacting in solution the API with the co-crystal former under crystallization conditions;

(4) isolating co-crystals formed thereby; and

(5) incorporating the co-crystals into a pharmaceutical composition.

In a still further aspect the present invention provides a process for the production of a pharmaceutical composition, which comprises:

(1) grinding, heating or contacting in solution an API with a co-crystal former, under crystallization conditions, so as to form a solid phase;

(2) isolating co-crystals comprising the API and the co-crystal former; and

(3) incorporating the co-crystals into a pharmaceutical composition.

Assaying the solid phase for the presence of co-crystals of the API and the co-crystal former may be carried out by conventional methods known in the art. For example, it is convenient and routine to use powder X-ray diffraction techniques to assess the presence of co-crystals. This may be affected by comparing the spectra of the API, the crystal former and putative co-crystals in order to establish whether or not true co-crystals had been formed. Other techniques, used in an analogous fashion, include differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), solid state NMR spectroscopy, and Raman spectroscopy. Single crystal X-ray diffraction is especially useful in identifying co-crystal structures.

In a further aspect, the present invention therefore provides a process of screening for co-crystal compounds, which comprises:

(1) providing (*i*) an API compound, and (*ii*) a co-crystal former; and

(2) screening for co-crystals of APIs with co-crystal formers by subjecting each combination of API and co-crystal former to a step comprising:

(a) grinding, heating, co-subliming, co-melting, or contacting in solution the API with the co-crystal former under crystallization conditions so as to form a solid phase; and

(b) isolating co-crystals comprising the API and the co-crystal former.

An alternative embodiment is drawn to a process of screening for co-crystal compounds, which comprises:

(1) providing (*i*) an API or a plurality of different APIs, and (*ii*) a co-crystal former or a plurality of different co-crystal formers, wherein at least one of the API and the co-crystal former is provided as a plurality thereof; and

(2) screening for co-crystals of APIs with co-crystal formers by subjecting each combination of API and co-crystal former to a step comprising

(a) grinding, heating, co-subliming, co-melting, or contacting in solution the API with the co-crystal former under crystallization conditions so as to form a solid phase; and

(b) isolating co-crystals comprising the API and the co-crystal former.

Some of the APIs and co-crystal formers of the present invention have one or more chiral centers and may exist in a variety of stereoisomeric configurations. As a consequence of these chiral centers, several APIs and co-crystal formers of the present invention occur as racemates, mixtures of enantiomers and as individual enantiomers, as well as diastereomers and mixtures of diastereomers. All such racemates, enantiomers, and diastereomers are within the scope of the present invention including, for example, *cis*- and *trans*-isomers, R- and S-enantiomers, and (D)- and (L)-isomers. Co-crystals of the present invention can include isomeric forms of either the API or the co-crystal former or both. Isomeric forms of APIs and co-crystal formers include, but are not limited to, stereoisomers such as enantiomers and diastereomers. In one embodiment, a co-crystal can comprise a racemic API and/or co-crystal former. In another embodiment, a co-crystal can comprise an enantiomerically pure API and/or co-crystal former. In another embodiment, a co-crystal can comprise an API or a co-crystal former with an enantiomeric excess of about 50 percent, 55 percent, 60 percent, 65 percent, 70 percent, 75 percent, 80 percent, 85 percent, 90 percent, 95 percent, 96 percent, 97 percent, 98 percent, 99 percent, greater than 99 percent, or any intermediate value. Several non-limiting examples of stereoisomeric APIs include modafinil, *cis*-itraconazole, ibuprofen, and flurbiprofen. Several non-limiting examples of stereoisomeric co-crystal formers

include tartaric acid and malic acid.

Co-crystals comprising enantiomerically pure components (e.g., API or co-crystal former) can give rise to chemical and/or physical properties which are modulated with respect to those of the corresponding co-crystal comprising a racemic component. For example, the modafinil:malonic acid co-crystal from Example 10 comprises racemic modafinil. Enantiomerically pure R-modafinil:malonic acid can conceivably be synthesized via the same or another method of the present invention and is therefore included in the scope of the invention. Likewise, enantiomerically pure S-modafinil:malonic acid can conceivably be synthesized via a method of the present invention and is therefore included in the scope of the invention. A co-crystal comprising an enantiomerically pure component can give rise to a modulation of, for example, activity, bioavailability, or solubility, with respect to the corresponding co-crystal comprising a racemic component. As an example, the co-crystal R-modafinil:malonic acid can have modulated properties as compared to the racemic modafinil:malonic acid co-crystal.

As used herein and unless otherwise noted, the term "racemic co-crystal" refers to a co-crystal which is comprised of an equimolar mixture of two enantiomers of the API, the co-crystal former, or both. For example, a co-crystal comprising a stereoisomeric API and a non-stereoisomeric co-crystal former is a "racemic co-crystal" when there is present an equimolar mixture of the API enantiomers. Similarly, a co-crystal comprising a non-stereoisomeric API and a stereoisomeric co-crystal former is a "racemic co-crystal" when there is present an equimolar mixture of the co-crystal former enantiomers. In addition, a co-crystal comprising a stereoisomeric API and a stereoisomeric co-crystal former is a "racemic co-crystal" when there is present an equimolar mixture of the API enantiomers and of the co-crystal former enantiomers.

As used herein and unless otherwise noted, the term "enantiomerically pure co-crystal" refers to a co-crystal which is comprised of a stereoisomeric API or a stereoisomeric co-crystal former or both where the enantiomeric excess of the stereoisomeric species is greater than or equal to about 90 percent *ee*.

In another embodiment, the present invention includes a pharmaceutical composition comprising a co-crystal with an enantiomerically pure API or co-crystal

former wherein the bioavailability is modulated with respect to the racemic co-crystal. In another embodiment, the present invention includes a pharmaceutical composition comprising a co-crystal with an enantiomerically pure API or co-crystal former wherein the activity is modulated with respect to the racemic co-crystal. In another embodiment, the present invention includes a pharmaceutical composition comprising a co-crystal with an enantiomerically pure API or co-crystal former wherein the solubility is modulated with respect to the racemic co-crystal.

As used herein, the term "enantiomerically pure" includes a composition which is substantially enantiomerically pure and includes, for example, a composition with greater than or equal to about 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 percent enantiomeric excess.

Solubility Modulation

In a further aspect, the present invention provides a process for modulating the solubility of an API, which process comprises:

(1) grinding, heating, co-subliming, co-melting, or contacting in solution the API with a co-crystal former under crystallization conditions, so as to form a co-crystal of the API and the co-crystal former; and

(2) isolating co-crystals comprising the API and the co-crystal former.

In one embodiment, the solubility of the API is modulated such that the aqueous solubility is increased. Solubility of APIs may be measured by any conventional means such as chromatography (e.g., HPLC) or spectroscopic determination of the amount of API in a saturated solution of the API, such as UV-spectroscopy, IR-spectroscopy, Raman spectroscopy, quantitative mass spectroscopy, or gas chromatography.

In another aspect of the invention, the API may have low aqueous solubility. Typically, low aqueous solubility in the present application refers to a compound having a solubility in water which is less than or equal to 10 mg/mL, when measured at 37 degrees C, and preferably less than or equal to 5 mg/mL or 1 mg/mL. Low aqueous solubility can further be specifically defined as less than or equal to 900, 800, 700, 600, 500, 400, 300, 200 150 100, 90, 80, 70, 60, 50, 40, 30, 20 micrograms/mL, or further 10,

5 or 1 micrograms/mL, or further 900, 800, 700, 600, 500, 400, 300, 200 150, 100 90, 80, 70, 60, 50, 40, 30, 20, or 10 ng/mL, or less than 10 ng/mL when measured at 37 degrees C. Aqueous solubility can also be specified as less than 500, 400, 300, 200, 150, 100, 75, 50 or 25 mg/mL. As embodiments of the present invention, solubility can be increased 2, 3, 4, 5, 7, 10, 15, 20, 25, 50, 75, 100, 200, 300, 500, 750, 1000, 5000, or 10,000 times by making a co-crystal of the reference form (e.g., crystalline or amorphous free acid, free base or zwitter ion, hydrate or solvate), or a salt thereof. Further aqueous solubility can be measured in simulated gastric fluid (SGF) or simulated intestinal fluid (SIF) rather than water. SGF (non-diluted) of the present invention is made by combining 1 g/L Triton X-100 and 2 g/L NaCl in water and adjusting the pH with 20 mM HCl to obtain a solution with a final pH=1.7 (SIF is 0.68% monobasic potassium phosphate, 1% pancreatin, and sodium hydroxide where the pH of the final solution is 7.5). The pH of the solvent used may also be specified as 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, 11.5, 12, 12.5, 13, 13.5, or 14 or any pH in between successive values.

Examples of embodiments includes: co-crystal compositions with an aqueous solubility, at 37 degrees C and a pH of 7.0, that is increased at least 5 fold over the reference form, co-crystal compositions with a solubility in SGF that is increased at least 5 fold over the reference form, co-crystal compositions with a solubility in SIF that is increased at least 5 fold over the reference form.

Dissolution Modulation

In another aspect of the present invention, the dissolution profile of the API is modulated whereby the aqueous dissolution rate or the dissolution rate in simulated gastric fluid or in simulated intestinal fluid, or in a solvent or plurality of solvents is increased. Dissolution rate is the rate at which API solids dissolve in a dissolution medium. For APIs whose absorption rates are faster than the dissolution rates (e.g., steroids), the rate-limiting step in the absorption process is often the dissolution rate. Because of a limited residence time at the absorption site, APIs that are not dissolved before they are removed from intestinal absorption site are considered useless. Therefore, the rate of dissolution has a major impact on the performance of APIs that are poorly

soluble. Because of this factor, the dissolution rate of APIs in solid dosage forms is an important, routine, quality control parameter used in the API manufacturing process.

$$\text{Dissolution rate} = K\,S\,(C_s - C)$$

where K is dissolution rate constant, S is the surface area, C_s is the apparent solubility, and C is the concentration of API in the dissolution medium. For rapid API absorption, C_s-C is approximately equal to C_s. The dissolution rate of APIs may be measured by conventional means known in the art.

The increase in the dissolution rate of a co-crystal, as compared to the reference form (e.g., free form or salt), may be specified, such as by 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100%, or by 2, 3, 4, 5 ,6, 7, 8, 9, 10, 15, 20, 25, 30, 40, 50, 75, 100, 125, 150, 175, 200, 250, 300, 350, 400, 500, 1000, 10,000, or 100,000 fold greater than the reference form (e.g., free form or salt form) in the same solution. Conditions under which the dissolution rate is measured is the same as discussed above The increase in dissolution may be further specified by the time the composition remains supersaturated before reaching equilibrium solubility.

Examples of above embodiments include: co-crystal compositions with a dissolution rate in aqueous solution, at 37 degrees C and a pH of 7.0, that is increased at least 5 fold over the reference form, co-crystal compositions with a dissolution rate in SGF that is increased at least 5 fold over the reference form, co-crystal compositions with a dissolution rate in SIF that is increased at least 5 fold over the reference form.

Bioavailability Modulation

The methods of the present invention are used to make a pharmaceutical API formulation with greater solubility, dissolution, and bioavailability. Bioavailability can be improved via an increase in AUC, reduced time to T_{max}, (the time to reach peak blood serum levels), or increased C_{max},. The present invention can result in higher plasma concentrations of API when compared to the neutral form or salt alone (reference form). AUC is the area under the plot of plasma concentration of API (not logarithm of the concentration) against time after API administration. The area is conveniently determined by the "trapezoidal rule": The data points are connected by straight line segments, perpendiculars are erected from the abscissa to each data point, and the sum of the areas

of the triangles and trapezoids so constructed is computed. When the last measured concentration (C_n, at time t_n) is not zero, the AUC from t_n to infinite time is estimated by C_n/k_{el}.

The AUC is of particular use in estimating bioavailability of APIs, and in estimating total clearance of APIs (Cl_T). Following single intravenous doses, AUC = D/Cl_T, for single compartment systems obeying first-order elimination kinetics, where D is the dose; alternatively, AUC = C_0/k_{el}, where k_{el} is the API elimination rate constant. With routes other than the intravenous, for such systems, AUC = $F \cdot D/Cl_T$, where F is the absolute bioavailability of the API.

Thus, in a further aspect, the present invention provides a process for modulating the bioavailability of an API when administered in its normal and effective dose range as a co-crystal, whereby the AUC is increased, the time to T_{max} is reduced, or C_{max} is increased, as compared to a reference form, which process comprises:

(1) grinding, heating, co-subliming, co-melting, or contacting in solution the API with a co-crystal former under crystallization conditions, so as to form a co-crystal of the API and the co-crystal former; and

(2) isolating co-crystals comprising the API and the co-crystal former.

Examples of the above embodiments include: co-crystal compositions with a time to T_{max} that is reduced by at least 10% as compared to the reference form, co-crystal compositions with a time to T_{max} that is reduced by at least 20% over the reference form, co-crystal compositions with a time to T_{max} that is reduced by at least 40% over the reference form, co-crystal compositions with a time to T_{max} that is reduced by at least 50% over the reference form, co-crystal compositions with a T_{max} that is reduced by at least 60% over the reference form, co-crystal compositions with a T_{max} that is reduced by at least 70% over the reference form, co-crystal compositions with a T_{max} that is reduced by at least 80% over the reference form, co-crystal compositions with a T_{max} that is reduced by at least 90% over the reference form, co-crystal compositions with a C_{max} that is increased by at least 20% over the reference form, co-crystal compositions with a C_{max} that is increased by at least 30% over the reference form, co-crystal compositions with a C_{max} that is increased by at least 40% over the reference form, co-crystal compositions

with a C_{max} that is increased by at least 50% over the reference form, co-crystal compositions with a C_{max} that is increased by at least 60% over the reference form, co-crystal compositions with a C_{max} that is increased by at least 70% over the reference form, co-crystal compositions with a C_{max} that is increased by at least 80% over the reference form, co-crystal compositions with a Cmax that is increased by at least 2 fold, 3 fold, 5 fold, 7.5 fold, 10 fold, 25 fold, 50 fold or 100 fold, co-crystal compositions with an AUC that is increased by at least 10% over the reference form, co-crystal compositions with an AUC that is increased by at least 20% over the reference form, co-crystal compositions with an AUC that is increased by at least 30% over the reference form, co-crystal compositions with an AUC that is increased by at least 40% over the reference form, co-crystal compositions with an AUC that is increased by at least 50% over the reference form, co-crystal compositions with an AUC that is increased by at least 60% over the reference form, co-crystal compositions with an AUC that is increased by at least 70% over the reference form, co-crystal compositions with an AUC that is increased by at least 80% over the reference form or co-crystal compositions with an AUC that is increased by at least 2 fold, 3 fold, 4 fold, 5 fold, 6 fold, 7 fold, 8 fold, 9 fold, or 10 fold. Other examples include wherein the reference form is crystalline, wherein the reference form is amorphous, wherein the reference form is an anhydrous crystalline sodium salt, or wherein the reference form is an anhydrous crystalline HCl salt.

Dose Response Modulation

In a further aspect the present invention provides a process for improving the dose response of an API, which process comprises:

(1) grinding, heating, co-subliming, co-melting, or contacting in solution an API with a co-crystal former under crystallization conditions, so as to form a co-crystal of the API and the co-crystal former; and

(2) isolating co-crystals comprising the API and the co-crystal former.

Dose response is the quantitative relationship between the magnitude of response and the dose inducing the response and may be measured by conventional means known in the art. The curve relating effect (as the dependent variable) to dose (as the

independent variable) for an API-cell system is the "dose-response curve". Typically, the dose-response curve is the measured response to an API plotted against the dose of the API (mg/kg) given. The dose response curve can also be a curve of AUC against the dose of the API given.

In an embodiment of the present invention, a co-crystal of the present invention has an increased dose response curve or a more linear dose response curve than the corresponding reference compound.

Increased Stability

In a still further aspect the present invention provides a process for improving the stability of an API (as compared to a reference form such as its free form or a salt thereof), which process comprises:

(1) grinding, heating, co-subliming, co-melting, or contacting in solution the pharmaceutical salt with a co-crystal former under crystallization conditions, so as to form a co-crystal of the API and the co-crystal former; and

(2) isolating co-crystals comprising the API and the co-crystal former.

In a preferred embodiment, the compositions of the present invention, including the API or active pharmaceutical ingredient (API) and formulations comprising the API, are suitably stable for pharmaceutical use. Preferably, the API or formulations thereof of the present invention are stable such that when stored at 30 degrees C for 2 years, less than 0.2 % of any one degradant is formed. The term degradant refers herein to product(s) of a single type of chemical reaction. For example, if a hydrolysis event occurs that cleaves a molecule into two products, for the purpose of the present invention, it would be considered a single degradant. More preferably, when stored at 40 degrees C for 2 years, less than 0.2 % of any one degradant is formed. Alternatively, when stored at 30 degrees C for 3 months, less than 0.2% or 0.15 %, or 0.1 % of any one degradant is formed, or when stored at 40 degrees C for 3 months, less than 0.2 % or 0.15 %, or 0.1 % of any one degradant is formed. Further alternatively, when stored at 60 degrees C for 4 weeks, less than 0.2 % or 0.15 %, or 0.1 % of any one degradant is formed. The relative humidity (RH) may be specified as ambient (RH), 75 % (RH), or as any single integer between 1 to 99 %.

Difficult to Salt or Unsaltable Compounds

In a still further aspect the present invention provides a process for making co-crystals of unsaltable or difficult to salt APIs which process comprises:

(1) grinding, heating, co-subliming, co-melting, or contacting in solution an API with a co-crystal former under crystallization conditions, so as to form a co-crystal of the API and the co-crystal former; and

(2) isolating co-crystals comprising the API and the co-crystal former.

Difficult to salt compounds include bases with a pKa less than 3 or acids with a pKa greater than 10. Zwitter ions are also difficult to salt or unsaltable compounds according to the present invention.

Decreasing Hygroscopicity

In a still further aspect, the present invention provides a method for decreasing the hygroscopicity of an API, which method comprises:

(1) grinding, heating, co-subliming, co-melting, or contacting in solution the API with a co-crystal former under crystallization conditions, so as to form a co-crystal of the API and the co-crystal former; and

(2) isolating co-crystals comprising the API and the co-crystal former.

An aspect of the present invention provides a pharmaceutical composition comprising a co-crystal of an API that is less hygroscopic than amorphous or crystalline, free form or salt (including metal salts such as sodium, potassium, lithium, calcium, magnesium) or another reference compound. Hygroscopicity can be assessed by dynamic vapor sorption analysis, in which 5-50 mg of the compound is suspended from a Cahn microbalance. The compound being analyzed should be placed in a non-hygroscopic pan and its weight should be measured relative to an empty pan composed of identical material and having nearly identical size, shape, and weight. Ideally, platinum pans should be used. The pans should be suspended in a chamber through which a gas, such as air or nitrogen, having a controlled and known percent relative humidity (%RH) is flowed until eqilibrium criteria are met. Typical equilibrium criteria include weight

changes of less than 0.01 % over 3 minutes at constant humidity and temperature. The relative humidity should be measured for samples dried under dry nitrogen to constant weight (<0.01 % change in 3 minutes) at 40 degrees C unless doing so would de-solvate or otherwise convert the material to an amorphous compound. In one aspect, the hygroscopicity of a dried compound can be assessed by increasing the RH from 5 to 95 % in increments of 5 % RH and then decreasing the RH from 95 to 5 % in 5 % increments to generate a moisture sorption isotherm. The sample weight should be allowed to equilibrate between each change in % RH. If the compound deliquesces or becomes amorphous above 75 % RH, but below 95 % RH, the experiment should be repeated with a fresh sample and the relative humidity range for the cycling should be narrowed to 5-75 % RH or 10-75 % RH, instead of 5-95 %RH. If the sample cannot be dried prior to testing due to lack of form stability, than the sample should be studied using two complete humidity cycles of either 10-75 % RH or 5-95 % RH, and the results of the second cycle should be used if there is significant weight loss at the end of the first cycle. Hygroscopicity can be defined using various parameters. For purposes of the present invention, a non-hygroscopic molecule should not gain or lose more than 1.0 %, or more preferably, 0.5 % weight at 25 degrees C when cycled between 10 and 75 % RH (relative humidity at 25 degrees C). The non-hygroscopic molecule more preferably should not gain or lose more than 1.0 %, or more preferably, 0.5 % weight when cycled between 5 and 95 % RH at 25 degrees C, or more than 0.25 % of its weight between 10 and 75 % RH. Most preferably, a non-hygroscopic molecule will not gain or lose more than 0.25 % of its weight when cycled between 5 and 95 % RH.

Alternatively, for purposes of the present invention, hygroscopicity can be defined using the parameters of Callaghan et al., "Equilibrium moisture content ofpharmaceutical excipients", in Api Dev. Ind. Pharm., Vol. 8, pp. 335-369 (1982). Callaghan et al. classified the degree of hygroscopicity into four classes.

Class 1: Non-hygroscopic Essentially no moisture increases occur at relative humidities below 90 %.

Class 2: Slightly hygroscopic Essentially no moisture increases occur at relative humidities below 80%.

Class 3: Moderately hygroscopic Moisture content does not inerease more than 5 % after storage for 1 week at relative humidities below 60 %.

Class 4: Very hygroscopic Moisture content increase may occur at relative humidities as low as 40 to 50 %.

Alternatively, for purposes of the present invention, hygroscopicity can be defined using the parameters of the European Pharmacopoeia Technical Guide (1999, p. 86) which has defined hygrospocity, based on the static method, after storage at 25 degrees C for 24 hours at 80 % RH:

Slightly hygroscopic: Increase in mass is less than 2 percent m/m and equal to or greater than 0.2 percent m/m.

Hygroscopic: Increase in mass is less than 15 percent m/m and equal to or greater than 0.2 percent m/m.

Very Hygroscopic: Increase in mass is equal to or greater than 15 percent m/m.

Deliquescent: Sufficient water is absorbed to form a liquid.

Co-crystals of the present invention can be set forth as being in Class 1, Class 2, or Class 3, or as being Slightly hygroscopic, Hygroscopic, or Very Hygroscopic. Co-crystals of the present invention can also be set forth based on their ability to reduce hygroscopicity. Thus, preferred co-crystals of the present invention are less hygroscopic than a reference compound. The reference compound can be specified as the API in free form (free acid, free base, hydrate, solvate, etc.) or salt (e.g., especially metal salts such as sodium, potassium, lithium, calcium, or magnesium). Further included in the present invention are co-crystals that do not gain or lose more than 1.0 % weight at 25 degrees C when cycled between 10 and 75 % RH, wherein the reference compound gains or loses more than 1.0 % weight under the same conditions. Further included in the present invention are co-crystals that do not gain or lose more than 0.5 % weight at 25 degrees C when cycled between 10 and 75 % RH, wherein the reference compound gains or loses more than 0.5 % or more than 1.0 % weight under the same conditions. Further included

in the present invention are co-crystals that do not gain or lose more than 1.0 % weight at 25 degrees C when cycled between 5 and 95 % RH, wherein the reference compound gains or loses more than 1.0 % weight under the same conditions. Further included in the present invention are co-crystals that do not gain or lose more than 0.5 % weight at 25 degrees C when cycled between 5 and 95 % RH, wherein the reference compound gains or loses more than 0.5 % or more than 1.0 % weight under the same conditions. Further included in the present invention are co-crystals that do not gain or lose more than 0.25 % weight at 25 degrees C when cycled between 5 and 95 % RH, wherein the reference compound gains or loses more than 0.5 % or more than 1.0 % weight under the same conditions.

Further included in the present invention are co-crystals that have a hygroscopicity (according to Callaghan et al.) that is at least one class lower than the reference compound or at least two classes lower than the reference compound. Included are a Class 1 co-crystal of a Class 2 reference compound, a Class 2 co-crystal of a Class 3 reference compound, a Class 3 co-crystal of a Class 4 reference compound, a Class 1 co-crystal of a Class 3 reference compound, a Class 1 co-crystal of a Class 4 reference compound, or a Class 2 co-crystal of a Class 4 reference compound.

Further included in the present invention are co-crystals that have a hygroscopicity (according to the European Pharmacopoeia Technical Guide) that is at least one class lower than the reference compound or at least two classes lower than the reference compound. Non-limiting examples include; a slightly hygroscopic co-crystal of a hygroscopic reference compound, a hygroscopic co-crystal of a very hygroscopic reference compound, a very hygroscopic co-crystal of a deliquescent reference compound, a slightly hygroscopic co-crystal of a very hygroscopic reference compound, a slightly hygroscopic co-crystal of a deliquescent reference compound, and a hygroscopic co-crystal of a deliquescent reference compound.

Crystallizing Amorphous Compounds

In a further aspect, the present invention provides a process for crystallizing an amorphous compound, which process comprises:

(1) grinding, heating, co-subliming, co-melting, or contacting in solution the API with a co-crystal former under crystallization conditions, so as to form a co-crystal of the API and the co-crystal former; and

(2) isolating co-crystals comprising the API and the co-crystal former.

An amorphous compound includes compounds that do not crystallize using routine methods in the art.

Decreasing Form Diversity

In a still further embodiment aspect the present invention provides a process for reducing the form diversity of an API, which process comprises:

(1) grinding, heating, co-subliming, co-melting, or contacting in solution the API with a co-crystal former under crystallization conditions, so as to form a co-crystal of the API and the co-crystal former; and

(2) isolating co-crystals comprising the API and the co-crystal former.

For purposes of the present invention, the number of forms of a co-crystal is compared to the number of forms of a reference compound (e.g. the free form or a salt of the API) that can be made using routine methods in the art.

Morphology Modulation

In a still further aspect the present invention provides a process for modifying the morphology of an API, which process comprises:

(1) grinding, heating, co-subliming, co-melting, or contacting in solution the API with a co-crystal former under crystallization conditions, so as to form a co-crystal of the API and the co-crystal former; and

(2) isolating co-crystals comprising the API and the co-crystal former.

In an embodiment the co-crystal comprises or consists of a co-crystal former and a pharmaceutical wherein the interaction between the two, e.g., H-bonding, occurs between a functional group of Table III of an API with a corresponding interacting group of Table III. In a further embodiment, the co-crystal comprises a co-crystal former of

Table I or II and an API with a corresponding interacting group of Table III. In a further embodiment the co-crystal comprises an API from Table IV and a co-crystal former with a functional group of Table III. In a further embodiment, the co-crystal is from Table I or II. In an aspect of the invention, only co-crystals having an H-bond acceptor on the first molecule and an H-bond donor on the second molecule, where the first and second molecules are either co-crystal former and API respectively or API and co-crystal former respectively, are included in the present invention. Table IV includes the CAS number, chemical name or a PCT or patent reference (each incorporated herein in their entireties). Thus, whether a particular API contains an H-bond donor, acceptor or both is readily apparent.

In another embodiment, the co-crystal former and API each have only one H-bond donor/acceptor. In another aspect, the molecular weight of the API is less than 2000, 1500, 1000, 750, 500, 350, 200, or 150 Daltons. In another embodiment, the molecular weight of the API is between 100-200, 200-300, 300-400, 400-500, 500-600, 600-700, 700-800, 800-900, 900-1000, 1000-1200, 1200-1400, 1400-1600, 1600-1800, or 1800-2000. APIs with the above molecular weights may also be specifically excluded from the present invention.

The hydrogen bond donor moieties of a co-crystal can include, but are not limited to, any one, any two, any three, any four, or more of the following: amino-pyridine, primary amine, secondary amine, sulfonamide, primary amide, secondary amide, alcohol, and carboxylic acid. The hydrogen bond acceptor moieties of a co-crystal can include, but are not limited to, any one, any two, any three, any four, or more of the following: amino-pyridine, primary amine, secondary amine, sulfonamide, primary amide, secondary amide, alcohol, carboxylic acid, carbonyl, cyano, dimethoxyphenyl, sulfonyl, aromatic nitrogen (6 membered ring), ether, chloride, organochloride, bromide, organobromide, and organoiodide. Hydrogen bonds are known to form many supramolecular structures including, but not limited to, a catemer, a dimer, a trimer, a tetramer, or a higher order structure. Tables V-XXI list specific hydrogen bond donor and acceptor moieties and their approximate interaction distances from the electromagnetic donor atom through the hydrogen atom to the electromagnetic acceptor atom. For example, Table V lists functional groups that are known to hydrogen bond

with amino-pyridines. Amino-pyridines comprise two distinct sites of hydrogen bond donation/acceptance. Both the aromatic nitrogen atom (Npy) and the amine group (NH_2) can participate in hydrogen bonds. The ability of a given functional group to participate in a hydrogen bond as a donor or as an acceptor or both can be determined by inspection by those skilled in the art.

The data included in Tables V-XXI are taken from an analysis of solid-state structures as reported in the Cambridge Structural Database (CSD). These data include a number of hydrogen bonding interactions between many functional groups and their associated interaction distances.

Table V- Hydrogen bonding functional groups with amino-pyridines and associated interaction distances

Functional Group	Interaction Distances (angstroms)	Mean	Standard Deviation
Primary Amide (to NH_2)	3.07	N/A	N/A
Primary Amide (to Npy)	2.97	N/A	N/A
Secondary Amide (to NH_2)	2.75-3.17	N/A	N/A
Secondary Amide (to Npy)	2.70-3.20	2.92	0.07
Carboxylic Acid (to NH_2)	2.72-3.07	2.89	0.08
Carboxylic Acid (to Npy)	2.54-2.82	2.67	0.05
Water (to NH_2)	2.72-3.15	2.94	0.09
Water (to Npy)	2.65-3.15	2.87	0.10
Alcohol (to NH_2)	2.78-3.14	2.96	0.08
Alcohol (to Npy)	2.63-3.06	2.79	0.07
Primary Amine	2.85-3.25	3.05	0.07
Secondary Amine	2.83-3.25	2.93	0.05
Carbonyl	2.87-3.10	2.95	0.07
Sulfoxo	2.70-3.10	2.90	0.08
Ether	2.84-3.20	3.05	0.07
Ester (C-O-C)	3.09	N/A	N/A
Ester (C=O)	2.85-3.16	3.00	0.08
Aromatic N	2.78-3.25	3.04	0.07
Cyano	2.83-3.30	3.09	0.12
Nitro	2.85-3.28	3.08	0.11
Chloride	3.10-3.45	3.25	0.08
Bromide	3.27-3.48	3.39	0.05

Table VI- Hydrogen bonding functional groups with primary amines and associated interaction distances

Functional Group	Interaction Distances (angstroms)	Mean	Standard Deviation
Primary Amide	2.73-3.20	2.98	0.13
Secondary Amide	2.65-3.20	2.97	0.09
Carboxylic Acid (O=C)	2.74-3.15	2.94	0.09

Carboxylic Acid (OH)	2.72-3.12	2.95	0.11
Amino-pyridine	3.10-3.24	3.22	0.02
Sulfonamide	2.86-3.17	3.02	0.11
Water	2.65-3.17	2.95	0.10
Alcohol	2.63-3.26	2.98	0.15
Carbonyl	2.64-3.15	2.95	0.09
Sulfoxo	2.70-3.10	2.92	0.09
Sulfonyl	2.93-3.12	3.13	0.12
Ether	2.75-3.25	3.05	0.11
Ester (C-O-C)	2.90-3.20	3.11	0.07
Ester (O=C)	2.74-3.27	3.04	0.12
Aromatic N	2.92-3.26	3.07	0.07
Cyano	2.83-3.30	3.02	0.06
Nitro	2.75-3.17	3.05	0.08
Chloride	3.07-3.50	3.28	0.09
Bromide	3.23-3.60	3.43	0.08

Table VII- Hydrogen bonding functional groups with primary sulfonamides and associated interaction distances

Functional Group	Interaction Distances (angstroms)	Mean	Standard Deviation
Water	2.87	N/A	N/A
Alcohol	2.85-3.07	2.94	0.06
Primary Amine	2.85-3.20	3.02	0.10
Secondary Amine	2.85-3.20	3.03	0.10
Sulfonyl	2.85-3.20	3.03	0.12
Ether	2.90-3.20	3.07	0.08
Ester	2.85-3.12	2.99	0.07
Cyano	3.00	N/A	N/A
Nitro	3.00-3.20	3.12	0.07
Chloride	3.20-3.32	3.26	0.03

Table VIII- Hydrogen bonding functional groups with primary amides and associated interaction distances

Functional Group	Interaction Distances (angstroms)	Mean	Standard Deviation
Secondary Amide	2.70-3.15	2.935	0.07
Carboxylic Acid (OH)	2.40-2.80	2.560	0.06
Carboxylic Acid (C=O)	2.80-3.25	2.961	0.09
Amino-pyridine (NH_2)	2.90-3.20	3.069	0.00
Amino-pyridine (Aromatic N)	2.80-3.10	2.972	0.00
Aromatic N	2.90-3.21	3.069	0.07
Water (to C=O)	2.60-3.00	2.813	0.08
Water (to NH_2)	2.70-3.07	2.945	0.07
Alcohol (to C=O)	2.50-3.00	2.753	0.07
Alcohol (to NH_2)	2.70-3.10	2.965	0.06
Secondary Amine (to C=O)	2.80-3.10	2.967	0.07
Secondary Amine (to NH_2)	3.00-3.15	3.079	0.03
Carbonyl	2.80-3.15	2.993	0.08
Sulfonyl	2.90-3.00	2.920	0.00
Ether	2.80-3.10	2.960	0.07

Ester (C=O)	2.70-3.05	2.932	0.05
Cyano	3.00-3.30	3.117	0.07
Nitro	2.90-3.07	3.020	0.03
Chloride	3.10-3.60	3.340	0.08
Bromide	3.30-3.80	3.550	0.11

Table IX- Hydrogen bonding functional groups with secondary amides and associated interaction distances

Functional Group	Interaction Distances (angstroms)	Mean	Standard Deviation
Primary Amide	2.70-3.15	2.935	0.07
Carboxylic Acid (C=O)	2.70-3.10	2.920	0.09
Carboxylic Acid (OH)	2.40-3.05	2.606	0.05
Amino-pyridine (Aromatic N)	2.70-3.20	2.920	0.07
Amino-pyridine (NH_2)	2.75-3.17	2.920	0.08
Sulfonamide (S=O)	2.80-3.20	3.110	0.16
Sulfonamide (NH_2)	2.70-3.00	2.916	0.05
Aromatic N	2.60-3.15	2.955	0.09
Water (to C=O)	2.40-3.10	2.840	0.09
Water (to NH_2)	2.60-3.10	2.887	0.10
Alcohol (to C=O)	2.50-3.04	2.773	0.09
Alcohol (to NH_2)	2.50-3.20	2.933	0.11
Primary Amine	2.65-3.20	2.970	0.09
Secondary Amine	2.60-3.15	2.932	0.11
Carbonyl	2.70-3.07	2.937	0.08
Sulfonyl	2.60-3.25	3.080	0.09
Ether	2.70-3.16	2.992	0.09
Ester	2.80-3.16	2.986	0.09
Cyano	2.90-3.30	3.120	0.09
Nitro	2.80-3.10	2.993	0.08
Chloride	2.90-3.40	3.261	0.15
Bromide	3.10-3.50	3.394	0.11

Table X- Hydrogen bonding functional groups with alcohols and associated interaction distances

Functional Group	Interaction Distances (angstroms)	Mean	Standard Deviation
Primary Amide (C=O)	2.50-3.00	2.753	0.07
Primary Amide (NH_2)	2.70-3.10	2.965	0.06
Secondary Amide (C=O)	2.50-3.04	2.773	0.09
Secondary Amide (NH_2)	2.50-3.20	2.933	0.11
Carboxylic Acid (C=O)	2.50-3.00	2.792	0.08
Carboxylic Acid (OH)	2.40-2.90	2.649	0.05
Amino-pyridine (Aromatic N)	2.60-3.06	2.790	0.07
Amino-pyridine (NH_2)	2.75-3.15	2.960	0.08
Sulfonamide	2.80-3.07	2.940	0.06
Aromatic N	2.50-3.00	2.777	0.08
Water	2.40-3.03	2.787	0.10
Primary Amine	2.60-3.15	2.897	0.13
Secondary Amine	2.60-3.15	2.888	0.13
Carbonyl	2.40-3.05	2.805	0.11
Sulfonyl	2.40-3.15	2.870	0.10
Ether	2.40-3.00	2.841	0.08

Ester	2.50-3.10	2.852	0.10
Cyano	2.40-3.10	2.873	0.09
Nitro	2.45-3.05	2.935	0.08
Chloride	2.60-3.30	3.093	0.07
Bromide	3.00-3.50	3.258	0.07

Table XI- Hydrogen bonding functional groups with carboxylic acids and associated interaction distances

Functional Group	Interaction Distances (angstroms)	Mean	Standard Deviation
Primary Amide (NH_2)	2.80-3.25	2.961	0.09
Primary Amide (C=O)	2.40-2.80	2.560	0.07
Secondary Amide (NH)	2.70-3.10	2.920	0.09
Secondary Amide (C=O)	2.40-3.05	2.606	0.05
Amino-pyridine (Aromatic N)	2.50-2.80	2.670	0.05
Amino-pyridine (NH_2)	2.70-3.00	2.890	0.08
Aromatic N	2.54-2.94	2.658	0.06
Water (to C=O)	2.50-3.00	2.830	0.07
Water (to OH)	2.40-3.00	2.626	0.11
Alcohol (to C=O)	2.50-3.00	2.792	0.08
Alcohol (to OH)	2.50-2.90	2.649	0.05
Primary Amine (to C=O)	2.70-3.10	2.959	0.09
Primary Amine (to OH)	2.70-3.10	2.828	0.12
Secondary Amine (to C=O)	2.70-3.10	2.909	0.11
Secondary Amine (to OH)	2.70-3.10	2.727	0.12
Carbonyl	2.40-3.00	2.696	0.08
Ether	2.50-3.00	2.751	0.12
Ester (C=O)	2.40-3.05	2.672	0.07
Ester (C-O-C)	2.40-3.10	2.990	N/A
Cyano	2.50-2.80	2.746	0.09
Nitro	2.70-3.05	2.942	0.10
Chloride	2.80-3.20	3.001	0.05
Bromide	3.00-3.30	3.150	0.05

Table XII- Hydrogen bonding functional groups with carbonyls and associated interaction distances

Functional Group	Interaction Distances (angstroms)	Mean	Standard Deviation
Primary Amide	2.83-3.15	3.96	0.06
Secondary Amide	2.70-3.07	2.93	0.08
Carboxylic Acid	2.40-3.00	2.70	0.08
Amino-pyridine	2.87-3.10	2.95	0.07
Secondary Sulfonamide	2.76-3.22	2.949	0.12
Water	2.55-3.05	2.82	0.10
Alcohol	2.40-3.05	2.80	0.01
Primary Amine	2.64-3.15	2.959	0.09
Secondary Amine	2.64-3.15	2.87	0.01

Table XIII- Hydrogen bonding functional groups with cyano groups and associated interaction distances

Functional Group	Interaction Distances (angstroms)	Mean	Standard Deviation
Primary Amide	3.01-3.30	3.15	0.09
Secondary Amide	2.90-3.30	3.13	N/A
Carboxylic Acid	2.57-3.00	2.75	0.09
Amino-pyridine	2.84-3.33	3.10	0.12
Primary Sulfonamide	2.99	N/A	N/A
Secondary Sulfonamide	2.83-3.00	2.90	0.07
Water	2.78-3.20	2.98	0.01
Alcohol	2.72-3.13	2.89	0.09
Primary Amine	2.84-3.27	3.08	0.09
Secondary Amine	2.84-3.30	3.09	0.12

Table XIV- Hydrogen bonding functional groups with sulfonyl groups and associated interaction distances

Functional Group	Interaction Distances (angstroms)	Mean	Standard Deviation
Primary Amide	2.92	N/A	N/A
Secondary Amide	2.95-3.25	3.08	0.09
Primary Sulfonamide	2.85-3.10	3.00	0.10
Secondary Sulfonamide	2.85-3.20	3.04	N/A
Water	2.84-3.00	2.90	0.05
Alcohol	2.65-3.15	2.87	0.1
Primary Amine	2.93-3.32	3.13	0.12
Secondary Amine	2.75-3.32	3.05	0.12

Table XV- Hydrogen bonding functional groups with aromatic N and associated interaction distances

Functional Group	Interaction Distances (angstroms)	Mean	Standard Deviation
Primary Amide	2.90-3.21	3.07	0.07
Secondary Amide	2.60-3.15	2.96	0.09
Carboxylic Acid	2.54-2.94	2.66	0.06
Amino-pyridine	2.70-3.20	3.04	0.07
Water	2.60-3.15	2.91	0.09
Alcohol	2.50-3.00	2.78	0.08
Primary Amine	2.92-3.26	3.07	0.07
Secondary Amine	2.73-3.25	3.02	0.10

Table XVI- Hydrogen bonding functional groups with ethers and associated interaction distances

Functional Group	Interaction Distances (angstroms)	Mean	Standard Deviation
Primary Amide	2.80-3.10	2.97	0.08
Secondary Amide	2.70-3.16	2.99	0.09
Carboxylic Acid	2.50-3.02	2.75	0.12
Amino-pyridine	2.80-3.20	3.05	0.07
Sulfonamide	0-3.20	3.07	0.08
Water	2.40-3.15	2.94	0.12
Alcohol	2.40-3.00	2.84	0.08
Primary Amine	2.75-3.25	3.05	0.11
Secondary Amine	2.60-3.25	3.05	0.13

Table XVII- Hydrogen bonding functional groups with chlorides and associated interaction distances

Functional Group	Interaction Distances (angstroms)	Mean	Standard Deviation
Primary Amide	3.10-3.60	3.34	0.08
Secondary Amide	2.90-3.30	3.18	0.06
Carboxylic Acid	2.80-3.30	3.00	0.05
Amino-pyridine	3.10-3.45	3.25	0.08
Sulfonamide	0-3.35	3.26	0.03
Water	2.70-3.30	3.17	0.06
Alcohol	2.50-3.30	3.09	0.07
Primary Amine	3.00-3.50	3.28	0.09
Secondary Amine	2.90-3.40	3.20	0.10

Table XVIII- Hydrogen bonding functional groups with organochlorides and associated interaction distances

Functional Group	Interaction Distances (angstroms)	Mean	Standard Deviation
Primary Amide	3.18-3.21	3.20	0.02
Secondary Amide	3.20-3.27	3.25	0.03
Carboxylic Acid	2.90-3.23	3.17	0.07
Amino-pyridine	3.28-3.33	3.31	0.03
Sulfonamide	0-3.50	N/A	N/A
Water	2.79-3.26	3.14	0.15
Alcohol	2.90-3.29	3.17	0.09
Primary Amine	3.21-3.29	3.25	0.05
Secondary Amine	3.26-3.30	3.28	0.02

Table XIX- Hydrogen bonding functional groups with bromides and associated interaction distances

Functional Group	Interaction Distances (angstroms)	Mean	Standard Deviation
Primary Amide	3.30-3.80	3.55	0.11
Secondary Amide	3.10-3.80	3.39	0.11
Carboxylic Acid	3.00-3.30	3.15	0.05
Amino-pyridine	3.20-3.50	3.39	0.05
Alcohol	3.00-3.50	3.26	0.07
Primary Amine	3.20-3.60	3.43	0.08
Secondary Amine	3.10-3.60	3.38	0.10

Table XX- Hydrogen bonding functional groups with organobromides and associated interaction distances

Functional Group	Interaction Distances (angstroms)	Mean	Standard Deviation
Primary Amide	0-3.50	3.24	N/A
Secondary Amide	0-3.50	N/A	N/A
Carboxylic Acid	3.01-3.31	3.20	0.16
Amino-pyridine	0-3.50	3.38	N/A
Sulfonamide	0-3.50	N/A	N/A
Water	3.14-3.27	3.21	0.09
Alcohol	2.90-3.36	3.21	0.12
Primary Amine	0-3.50	3.38	N/A
Secondary Amine	3.20-3.39	3.30	0.12

Table XXI- Hydrogen bonding functional groups with organoiodides and associated interaction distances

Functional Group	Interaction Distances (angstroms)	Mean	Standard Deviation
Primary Amide	0-3.80	N/A	N/A
Secondary Amide	0-3.80	N/A	N/A
Carboxylic Acid	0-3.80	3.59	0.16
Amino-pyridine	0-3.80	3.42	N/A
Aromatic N	2.70-3.23	2.95	0.11
Alcohol	2.90-3.48	3.20	0.20
Primary Amine	3.25-3.42	3.34	0.11
Secondary Amine	2.71-2.87	2.79	0.08

In another embodiment, peptides, proteins, nucleic acids or other biological APIs are excluded from the present invention. In another embodiment, all non-pharmaceutically acceptable co-crystal formers are excluded from the present invention. In another embodiment, organometalic APIs are excluded from the present invention. In another embodiment, a co-crystal former comprising any one or more of the functional groups of Table III may be specifically excluded from the present invention. In another embodiment, any one or more of the co-crystal formers of Table I or II may be specifically excluded from the present invention. Any APIs currently known in the art may also be specifically excluded from the present invention. For example, carbamazepine, itraconazole, nabumetone, fluoxetine, acetaminophen and theophylline can each be specifically excluded from the present invention. In another embodiment, the API is not a salt, is not a non-metal salt, or is not a metal salt, e.g., sodium, potassium, lithium, calcium or magnesium. In another embodiment, the API is a salt, is a non-metal salt, or is a metal salt, e.g., sodium, potassium, lithium, calcium, magnesium. In one embodiment, the API does not contain a halogen. In one embodiment, the API does contain a halogen.

In another embodiment, any one or more of the APIs of Table IV may be specifically excluded from the present invention. Any APIs currently known in the art may also be specifically excluded from the present invention. For example, nabumetone:2,3-naphthalenediol, fluoxetine HCl:benzoic acid, fluoxetine HCl:succinic acid, acetaminophen:piperazine, acetaminophen:theophylline, theophylline:salicylic acid, theophylline:p-hydroxybenzoic acid, theophylline:sorbic acid, theophylline:1-hydroxy-2-naphthoic acid, theophylline:glycolic acid, theophylline:2,5-dihydroxybenzoic acid, theophylline:chloroacetic acid, bis(diphenylhydantoin):9-ethyladenine acetylacetone

solvate, bis(diphenylhydantoin):9-ethyladenine 2,4-pentanedione solvate, 5,5-diphenylbarbituric acid:9-ethyladenine, bis(diphenylhydantoin):9-ethyladenine, 4-aminobenzoic acid:4-aminobenzonitrile, sulfadimidine:salicylic acid, 8-hydroxyquinolinium 4-nitrobenzoate:4-nitrobenzoic acid, sulfaproxyline:caffeine, retro-inverso-isopropyl (2R,3S)-4-cyclohexyl-2-hydroxy-3-(N-((2R)-2-morpholinocarbonylmethyl-3-(1-naphthyl)propionyl)-L-histidylamino)butyrate:cinnamic acid monohydrate, benzoic acid:isonicotinamide, 3-(2-N',N'-(dimethylhydrazino)-4-thiazolylmethylthio)-N''-sulfamoylpropionamidine:maleic acid, diglycine hydrochloride ($C_2H_5NO_2$:$C_2H_6NO_2^+Cl^-$), octadecanoic acid:3-pyridinecarboxamide, *cis*-N-(3-methyl-1-(2-(1,2,3,4-tetrahydro)naphthyl)-piperidin-4-yl)-N-phenylpropanamide hydrochloride:oxalic acid, trans-N-(3-methyl-1-(2-(1,2,3,4-tetrahydro)naphthyl)-piperidin-4-ylium)-N-phenylpropanamide oxalate:oxalic acid dihydrate, bis(1-(3-((4-(2-isopropoxyphenyl)-1-piperazinyl)methyl)benzoyl)piperidine) succinate:succinic acid, bis(p-cyanophenyl)imidazolylmethane:succinic acid, *cis*-1-((4-(1-imidazolylmethyl)cyclohexyl)methyl)imidazole:succinic acid, (+)-2-(5,6-dimethoxy-1,2,3,4-tetrahydro-1-naphthyl)imidazoline:(+)-dibenzoyl-D-tartaric acid, raclopride:tartaric acid, 2,6-diamino-9-ethylpurine:5,5-diethylbarbituric acid, 5,5-diethylbarbituric acid:bis(2-aminopyridine), 5,5-diethylbarbituric acid:acetamide, 5,5-diethylbarbituric acid:KI_3, 5,5-diethylbarbituric acid:urea, bis(barbital):hexamethylphosphoramide, 5,5-diethylbarbituric acid:imidazole, barbital:1-methylimidazole, 5,5-diethylbarbituric acid:N-methyl-2-pyridone, 2,4-diamino-5-(3,4,5-trimethoxybenzyl)-pyrimidine:5,5-diethylbarbituric acid, bis(barbital):caffeine, bis(barbital):1-methylimidazole, bis(beta-cyclodextrin):bis(barbital) hydrate, tetrakis(beta-cyclodextrin):tetrakis(barbital), 9-ethyladenine:5,5-diethylbarbituric acid, barbital:N'-(*p*-cyanophenyl)-N-(*p*-iodophenyl)melamine, barbital:2-amino-4-(*m*-bromophenylamino)-6-chloro-1,3,5-triazine, 5,5-diethylbarbituric acid:N,N'-diphenylmelamine, 5,5-diethylbarbituric acid:N,N'-bis(*p*-chlorophenyl)melamine, N,N'-bis(*p*-bromophenyl)melamine:5,5-diethylbarbituric acid, 5,5-diethylbarbituric acid:N,N'-bis(*p*-iodophenyl)melamine, 5,5-diethylbarbituric acid:N,N'-bis(*p*-tolyl)melamine, 5,5-diethylbarbituric acid:N,N'-bis(*m*-tolyl)melamine, 5,5-diethylbarbituric acid:N,N'-bis(*m*-chlorophenyl)melamine, N,N'-Bis(*m*-methylphenyl)melamine:barbital, N,N'-bis(*m*-

chlorophenyl)melamine:barbital tetrahydrofuran solvate, 5,5-diethylbarbituric acid:N,N'-bis(*tert*-butyl)melamine, 5,5-diethylbarbituric acid:N,N'-di(*tert*-butyl)melamine, 6,6'-diquinolyl ether:5,5-diethylbarbituric acid, 5-*tert*-butyl-2,4,6-triaminopyrimidine:diethylbarbituric acid, N,N'-bis(4-carboxymethylphenyl)melamine:barbital ethanol solvate, N,N'-bis(4-*tert*-butylphenyl)melamine:barbital, tris(5,17-N,N'-bis(4-amino-6-(butylamino)-1,3,5-triazin-2-yl)diamino-11,23-dinitro-25,26,27,28-tetrapropoxycalix(4)arene):hexakis(diethylbarbituric acid) toluene solvate, N,N'-bis(*m*-fluorophenyl)melamine:barbital, N,N'-bis(*m*-bromophenyl)melamine:barbital acetone solvate, N,N'-bis(*m*-iodophenyl)melamine:barbital acetonitrile solvate, N,N'-bis(*m*-trifluoromethylphenyl)melamine:barbital acetonitrile solvate, aminopyrine:barbital, N,N'-bis(4-fluorophenyl)melamine:barbital, N,N'-bis(4-trifluoromethylphenyl)melamine:barbital, 2,4-diamino-5-(3,4,5-trimethoxybenzyl)pyrimidine:barbital, hydroxybutyrate:hydroxyvalerate, 2-aminopyrimidine:succinic acid, 1,3-bis(((6-methylpyrid-2-yl)amino)carbonyl)benzene:glutaric acid, 5-*tert*-butyl-2,4,6-triaminopyrimidine:diethylbarbituric acid, bis(dithiobiuret-S,S')nickel(II):diuracil, platinum 3,3'-dihydroxymethyl-2,2'-bipyridine dichloride:AgF_3CSO_3, 4,4'-bipyridyl:isophthalic acid, 4,4'-bipyridyl:1,4-naphthalenedicarboxylic acid, 4,4'-bipyridyl:1,3,5-cyclohexane-tricarboxylic acid, 4,4'-bipyridyl:tricaballylic acid, urotropin:azelaic acid, insulin:C8-HI (octanoyl-N^{ε}-LysB29-human insulin), isonicotinamide:cinnamic acid, isonicotinamide:3-hydroxybenzoic acid, isonicotinamide:3-N,N-dimethylaminobenzoic acid, isonicotinamide:3,5-bis(trifluoromethyl)-benzoic acid, isonicotinamide:d,l-mandelic acid, isonicotinamide:chloroacetic acid, isonicotinamide:fumaric acid monoethyl ester, isonicotinamide:12-bromododecanoic acid, isonicotinamide:fumaric acid, isonicotinamide:succinic acid, isonicotinamide:4-ketopimelic acid, isonicotinamide:thiodiglycolic acid, 1,3,5-cyclohexane-tricarboxylic acid:hexamethyltetramine, 1,3,5-cyclohexane-tricarboxylic acid:4,7-phenanthroline, 4,7-phenanthroline:oxalic acid, 4,7-phenanthroline:terephthalic acid, 4,7-phenanthroline:1,3,5-cyclohexane-tricarboxylic acid, 4,7-phenanthroline:1,4-naphthalenedicarboxylic

acid, pyrazine:methanoic acid, pyrazine:ethanoic acid, pyrazine:propanoic acid, pyrazine:butanoic acid, pyrazine:pentanoic acid, pyrazine:hexanoic acid, pyrazine:heptanoic acid, pyrazine:octanoic acid, pyrazine:nonanoic acid, pyrazine:decanoic acid, diammine-(deoxy-quanyl-quanyl-N^7,N^7)-platinum:tris(glycine) hydrate, 2-aminopyrimidine:p-phenylenediacetic acid, bis(2-aminopyrimidin-1-ium)fumarate:fumaric acid, 2-aminopyrimidine:indole-3-acetic acid, 2-aminopyrimidine:N-methylpyrrole-2-carboxylic acid, 2-aminopyrimidine:thiophen-2-carboxylic acid, 2-aminopyrimidine:(+)-camphoric acid, 2,4,6-Trinitrobenzoic acid:2-aminopyrimidine, 2-aminopyrimidine:4-aminobenzoic acid, 2-aminopyrimidine:bis(phenoxyacetic acid), 2-aminopyrimidine:(2,4-dichlorophenoxy)acetic acid, 2-aminopyrimidine:(3,4-dichlorophenoxy)acetic acid, 2-aminopyrimidine:indole-2-carboxylic acid, 2-aminopyrimidine:terephthalic acid, 2-aminopyrimidine:bis(2-nitrobenzoic acid), 2-aminopyrimidine:bis(2-aminobenzoic acid), 2-aminopyrimidine:3-aminobenzoic acid, 2-hexeneoic acid:isonicotinamide, 4-nitrobenzoic acid:isonicotinamide, 3,5-dinitrobenzoic acid:isonicotinamide:4-methylbenzoic acid, 2-amino-5-nitropyrimidine:2-amino-3-nitropyridine, 3,5-dinitrobenzoic acid:4-chlorobenzamide, 3-dimethylaminobenzoic acid:4-chlorobenzamide, fumaric acid:4-chlorobenzamide, oxine:4-nitrobenzoic acid, oxine:3,5-dinitrobenzoic acid, oxine:3,5-dinitrosalicylic acid, 3-[2-(N',N'-dimethylhydrazino)-4-thiazolylmethylthio]-N^2-sulfamoylpropionamidine:maleic acid, 5-fluorouracil:9-ethylhypoxanthine, 5-fluorouracil:cytosine dihydrate, 5-fluorouracil:theophylline monohydrate, stearic acid:nicotinamide, *cis*-1-{[4-(1-imidazolylmethyl)cyclohexyl]methyl}imidazole:succinic acid, CGS18320B:succinic acid, sulfaproxyline:caffeine, 4-aminobenzoic acid:4-aminobenzonitrile, 3,5-dinitrobenzoic acid:isonicotinamide:3-methylbenzoic acid, 3,5-dinitrobenzoic acid:isonicotinamide:4-(dimethylamino)benzoic acid, 3,5-dinitrobenzoic acid:isonicotinamide:4-hydroxy-3-methoxycinnamic acid, isonicotinamide:oxalic acid, isonicotinamide:malonic acid, isonicotinamide:succinic acid, isonicotinamide:glutaric acid, isonicotinamide:adipic acid, benzoic acid:isonicotinamide, mazapertine:succinate, betaine:dichloronitrophenol, betainepyridine:dichloronitrophenol, betainepyridine:pentachlorophenol, 4-{2-[1-(2-hydroxyethyl)-4-pyridylidene]-

ethylidene}-cyclo-hexa-2,5-dien-1-one:methyl 2,4-dihydroxybenzoate, 4-{2-[1-(2-hydroxyethyl)-4-pyridylidene]-ethylidene}-cyclo-hexa-2,5-dien-1-one:2,4-dihydroxypropiophenone, 4-{2-[1-(2-hydroxyethyl)-4-pyridylidene]-ethylidene}-cyclo-hexa-2,5-dien-1-one:2,4-dihydroxyacetophenone, squaric acid:4,4'-dipyridylacetylene, squaric acid:1,2-bis(4-pyridyl)ethylene, chloranilic acid:1,4-bis[(4-pyridyl)ethynyl]benzene, 4,4'-bipyridine:phthalic acid, 4,4'-dipyridylacetylene:phthalic acid, bis(pentamethylcyclopentadienyl)iron:bromanilic acid, bis(pentamethylcyclopentadienyl)iron:chloranilic acid, bis(pentamethylcyclopentadienyl)iron:cyananilic acid, pyrazinotetrathiafulvalene:chloranilic acid, phenol:pentafluorophenol, co-crystals of *cis*-itraconazole, and co-crystals of topiramate are specifically excluded from the present invention.

In another embodiment, a pharmaceutical composition can be formulated to contain an API in co-crystal form as micronized or nano-sized particles. More specifically, another embodiment couples the processing of a pure API to a co-crystal form with the process of making a controlled particle size for manipulation into a pharmaceutical dosage form. This embodiment combines two processing steps into a single step via techniques such as, but not limited to, grinding, alloying, or sintering (i.e., heating a powder mix). The coupling of these processes overcomes a serious limitation of having to isolate and store the bulk drug that is required for a formulation, which in some cases can be difficult to isolate (e.g., amorphous, chemically or physically unstable).

Excipients employed in pharmaceutical compositions of the present invention can be solids, semi-solids, liquids or combinations thereof. Preferably, excipients are solids. Compositions of the invention containing excipients can be prepared by any known technique of pharmacy that comprises admixing an excipient with an API or therapeutic agent. A pharmaceutical composition of the invention contains a desired amount of API per dose unit and, if intended for oral administration, can be in the form, for example, of a tablet, a caplet, a pill, a hard or soft capsule, a lozenge, a cachet, a dispensable powder, granules, a suspension, an elixir, a dispersion, or any other form reasonably adapted for such administration. If intended for parenteral administration, it can be in the form, for

example, of a suspension or transdermal patch. If intended for rectal administration, it can be in the form, for example, of a suppository. Presently preferred are oral dosage forms that are discrete dose units each containing a predetermined amount of the API, such as tablets or capsules.

In another embodiment, APIs with an inappropriate pH for transdermal patches can be co-crystallized with an appropriate co-crystal former, thereby adjusting its pH to an appropriate level for use as a transdermal patch. In another embodiment, an APIs pH level can be optimized for use in a transdermal patch via co-crystallization with an appropriate co-crystal former.

Non-limiting examples follow of excipients that can be used to prepare pharmaceutical compositions of the invention.

Pharmaceutical compositions of the invention optionally comprise one or more pharmaceutically acceptable carriers or diluents as excipients. Suitable carriers or diluents illustratively include, but are not limited to, either individually or in combination, lactose, including anhydrous lactose and lactose monohydrate; starches, including directly compressible starch and hydrolyzed starches (e.g., Celutab™ and Emdex™); mannitol; sorbitol; xylitol; dextrose (e.g., Cerelose™ 2000) and dextrose monohydrate; dibasic calcium phosphate dihydrate; sucrose-based diluents; confectioner's sugar; monobasic calcium sulfate monohydrate; calcium sulfate dihydrate; granular calcium lactate trihydrate; dextrates; inositol; hydrolyzed cereal solids; amylose; celluloses including microcrystalline cellulose, food grade sources of alpha- and amorphous cellulose (e.g., RexcelJ), powdered cellulose, hydroxypropylcellulose (HPC) and hydroxypropylmethylcellulose (HPMC); calcium carbonate; glycine; bentonite; block co-polymers; polyvinylpyrrolidone; and the like. Such carriers or diluents, if present, constitute in total about 5% to about 99%, preferably about 10% to about 85%, and more preferably about 20% to about 80%, of the total weight of the composition. The carrier, carriers, diluent, or diluents selected preferably exhibit suitable flow properties and, where tablets are desired, compressibility.

Lactose, mannitol, dibasic sodium phosphate, and microcrystalline cellulose (particularly Avicel PH microcrystalline cellulose such as Avicel PH 101), either individually or in combination, are preferred diluents. These diluents are chemically

compatible with many co-crystals described herein. The use of extragranular microcrystalline cellulose (that is, microcrystalline cellulose added to a granulated composition) can be used to improve hardness (for tablets) and/or disintegration time. Lactose, especially lactose monohydrate, is particularly preferred. Lactose typically provides compositions having suitable release rates of co-crystals, stability, pre-compression flowability, and/or drying properties at a relatively low diluent cost. It provides a high density substrate that aids densification during granulation (where wet granulation is employed) and therefore improves blend flow properties and tablet properties.

Pharmaceutical compositions of the invention optionally comprise one or more pharmaceutically acceptable disintegrants as excipients, particularly for tablet formulations. Suitable disintegrants include, but are not limited to, either individually or in combination, starches, including sodium starch glycolate (e.g., Explotab™ of PenWest) and pregelatinized corn starches (e.g., National™ 1551 of National Starch and Chemical Company, National™ 1550, and Colorcon™ 1500), clays (e.g., Veegum™ HV of R.T. Vanderbilt), celluloses such as purified cellulose, microcrystalline cellulose, methylcellulose, carboxymethylcellulose and sodium carboxymethylcellulose, croscarmellose sodium (e.g., Ac-Di-Sol™ of FMC), alginates, crospovidone, and gums such as agar, guar, locust bean, karaya, pectin and tragacanth gums.

Disintegrants may be added at any suitable step during the preparation of the composition, particularly prior to granulation or during a lubrication step prior to compression. Such disintegrants, if present, constitute in total about 0.2% to about 30%, preferably about 0.2% to about 10%, and more preferably about 0.2% to about 5%, of the total weight of the composition.

Croscarmellose sodium is a preferred disintegrant for tablet or capsule disintegration, and, if present, preferably constitutes about 0.2% to about 10%, more preferably about 0.2% to about 7%, and still more preferably about 0.2% to about 5%, of the total weight of the composition. Croscarmellose sodium confers superior intragranular disintegration capabilities to granulated pharmaceutical compositions of the present invention.

Pharmaceutical compositions of the invention optionally comprise one or more pharmaceutically acceptable binding agents or adhesives as excipients, particularly for tablet formulations. Such binding agents and adhesives preferably impart sufficient cohesion to the powder being tableted to allow for normal processing operations such as sizing, lubrication, compression and packaging, but still allow the tablet to disintegrate and the composition to be absorbed upon ingestion. Such binding agents may also prevent or inhibit crystallization or recrystallization of a co-crsytal of the present invention once the salt has been dissolved in a solution. Suitable binding agents and adhesives include, but are not limited to, either individually or in combination, acacia; tragacanth; sucrose; gelatin; glucose; starches such as, but not limited to, pregelatinized starches (e.g., National™ 1511 and National™ 1500); celluloses such as, but not limited to, methylcellulose and carmellose sodium (e.g., Tylose™); alginic acid and salts of alginic acid; magnesium aluminum silicate; PEG; guar gum; polysaccharide acids; bentonites; povidone, for example povidone K-15, K-30 and K-29/32; polymethacrylates; HPMC; hydroxypropylcellulose (e.g., Klucel™ of Aqualon); and ethylcellulose (e.g., Ethocel™ of the Dow Chemical Company). Such binding agents and/or adhesives, if present, constitute in total about 0.5% to about 25%, preferably about 0.75% to about 15%, and more preferably about 1% to about 10%, of the total weight of the pharmaceutical composition.

Many of the binding agents are polymers comprising amide, ester, ether, alcohol or ketone groups and, as such, are preferably included in pharmaceutical compositions of the present invention. Polyvinylpyrrolidones such as povidone K-30 are especially preferred. Polymeric binding agents can have varying molecular weight, degrees of crosslinking, and grades of polymer. Polymeric binding agents can also be copolymers, such as block co-polymers that contain mixtures of ethylene oxide and propylene oxide units. Variation in these units' ratios in a given polymer affects properties and performance. Examples of block co-polymers with varying compositions of block units are Poloxamer 188 and Poloxamer 237 (BASF Corporation).

Pharmaceutical compositions of the invention optionally comprise one or more pharmaceutically acceptable wetting agents as excipients. Such wetting agents are preferably selected to maintain the co-crystal in close association with water, a condition

that is believed to improve bioavailability of the composition. Such wetting agents can also be useful in solubilizing or increasing the solubility of co-crystals.

Non-limiting examples of surfactants that can be used as wetting agents in pharmaceutical compositions of the invention include quaternary ammonium compounds, for example benzalkonium chloride, benzethonium chloride and cetylpyridinium chloride, dioctyl sodium sulfosuccinate, polyoxyethylene alkylphenyl ethers, for example nonoxynol 9, nonoxynol 10, and degrees Ctoxynol 9, poloxamers (polyoxyethylene and polyoxypropylene block copolymers), polyoxyethylene fatty acid glycerides and oils, for example polyoxyethylene (8) caprylic/capric mono- and diglycerides (e.g., Labrasol™ of Gattefosse), polyoxyethylene (35) castor oil and polyoxyethylene (40) hydrogenated castor oil; polyoxyethylene alkyl ethers, for example polyoxyethylene (20) cetostearyl ether, polyoxyethylene fatty acid esters, for example polyoxyethylene (40) stearate, polyoxyethylene sorbitan esters, for example polysorbate 20 and polysorbate 80 (e.g., Tween™ 80 of ICI), propylene glycol fatty acid esters, for example propylene glycol laurate (e.g., Lauroglycol™ of Gattefosse), sodium lauryl sulfate, fatty acids and salts thereof, for example oleic acid, sodium oleate and triethanolamine oleate, glyceryl fatty acid esters, for example glyceryl monostearate, sorbitan esters, for example sorbitan monolaurate, sorbitan monooleate, sorbitan monopalmitate and sorbitan monostearate, tyloxapol, and mixtures thereof. Such wetting agents, if present, constitute in total about 0.25% to about 15%, preferably about 0.4% to about 10%, and more preferably about 0.5% to about 5%, of the total weight of the pharmaceutical composition.

Wetting agents that are anionic surfactants are preferred. Sodium lauryl sulfate is a particularly preferred wetting agent. Sodium lauryl sulfate, if present, constitutes about 0.25% to about 7%, more preferably about 0.4% to about 4%, and still more preferably about 0.5% to about 2%, of the total weight of the pharmaceutical composition.

Pharmaceutical compositions of the invention optionally comprise one or more pharmaceutically acceptable lubricants (including anti-adherents and/or glidants) as excipients. Suitable lubricants include, but are not limited to, either individually or in combination, glyceryl behapate (e.g., Compritol™ 888 of Gattefosse); stearic acid and salts thereof, including magnesium, calcium and sodium stearates; hydrogenated vegetable oils (e.g., Sterotex™ of Abitec); colloidal silica; talc; waxes; boric acid;

sodium benzoate; sodium acetate; sodium fumarate; sodium chloride; DL-leucine; PEG (e.g., Carbowax™ 4000 and Carbowax™ 6000 of the Dow Chemical Company); sodium oleate; sodium lauryl sulfate; and magnesium lauryl sulfate. Such lubricants, if present, constitute in total about 0. 1% to about 10%, preferably about 0.2% to about 8%, and more preferably about 0.25% to about 5%, of the total weight of the pharmaceutical composition.

Magnesium stearate is a preferred lubricant used, for example, to reduce friction between the equipment and granulated mixture during compression of tablet formulations.

Suitable anti-adherents include, but are not limited to, talc, cornstarch, DL-leucine, sodium lauryl sulfate and metallic stearates. Talc is a preferred anti-adherent or glidant used, for example, to reduce formulation sticking to equipment surfaces and also to reduce static in the blend. Talc, if present, constitutes about 0.1% to about 10%, more preferably about 0.25% to about 5%, and still more preferably about 0.5% to about 2%, of the total weight of the pharmaceutical composition.

Glidants can be used to promote powder flow of a solid formulation. Suitable glidants include, but are not limited to, colloidal silicon dioxide, starch, talc, tribasic calcium phosphate, powdered cellulose and magnesium trisilicate. Colloidal silicon dioxide is particularly preferred.

Other excipients such as colorants, flavors and sweeteners are known in the pharmaceutical art and can be used in pharmaceutical compositions of the present invention. Tablets can be coated, for example with an enteric coating, or uncoated. Compositions of the invention can further comprise, for example, buffering agents. Optionally, one or more effervescent agents can be used as disintegrants and/or to enhance organoleptic properties of pharmaceutical compositions of the invention. When present in pharmaceutical compositions of the invention to promote dosage form disintegration, one or more effervescent agents are preferably present in a total amount of about 30% to about 75%, and preferably about 45% to about 70%, for example about 60%, by weight of the pharmaceutical composition.

According to a particularly preferred embodiment of the invention, an effervescent agent, present in a solid dosage form in an amount less than that effective to

promote disintegration of the dosage form, provides improved dispersion of the API in an aqueous medium. Without being bound by theory, it is believed that the effervescent agent is effective to accelerate dispersion of the API from the dosage form in the gastrointestinal tract, thereby further enhancing absorption and rapid onset of therapeutic effect. When present in a pharmaceutical composition of the invention to promote intragastrointestinal dispersion but not to enhance disintegration, an effervescent agent is preferably present in an amount of about 1% to about 20%, more preferably about 2.5% to about 15%, and still more preferably about 5% to about 10%, by weight of the pharmaceutical composition.

An "effervescent agent" herein is an agent comprising one or more compounds which, acting together or individually, evolve a gas on contact with water. The gas evolved is generally oxygen or, most commonly, carbon dioxide. Preferred effervescent agents comprise an acid and a base that react in the presence of water to generate carbon dioxide gas. Preferably, the base comprises an alkali metal or alkaline earth metal carbonate or bicarbonate and the acid comprises an aliphatic carboxylic acid.

Non-limiting examples of suitable bases as components of effervescent agents useful in the invention include carbonate salts (e.g., calcium carbonate), bicarbonate salts (e.g., sodium bicarbonate), sesquicarbonate salts, and mixtures thereof. Calcium carbonate is a preferred base.

Non-limiting examples of suitable acids as components of effervescent agents and/or solid organic acids useful in the invention include citric acid, tartaric acid (as D-, L-, or D/L-tartaric acid), malic acid (as D-, L-, or DL-malic acid), maleic acid, fumaric acid, adipic acid, succinic acid, acid anhydrides of such acids, acid salts of such acids, and mixtures thereof. Citric acid is a preferred acid.

In a preferred embodiment of the invention, where the effervescent agent comprises an acid and a base, the weight ratio of the acid to the base is about 1:100 to about 100:1, more preferably about 1:50 to about 50:1, and still more preferably about 1:10 to about 10:1. In a further preferred embodiment of the invention, where the effervescent agent comprises an acid and a base, the ratio of the acid to the base is approximately stoichiometric.

Excipients which solubilize APIs typically have both hydrophilic and hydrophobic regions, or are preferably amphiphilic or have amphiphilic regions. One type of amphiphilic or partially-amphiphilic excipient comprises an amphiphilic polymer or is an amphiphilic polymer. A specific amphiphilic polymer is a polyalkylene glycol, which is commonly comprised of ethylene glycol and/or propylene glycol subunits. Such polyalkylene glycols can be esterified at their termini by a carboxylic acid, ester, acid anhyride or other suitable moiety. Examples of such excipients include poloxamers (symmetric block copolymers of ethylene glycol and propylene glycol; e.g., poloxamer 237), polyalkyene glycolated esters of tocopherol (including esters formed from a di- or multi-functional carboxylic acid; e.g., d-alpha-tocopherol polyethylene glycol-1000 succinate), and macrogolglycerides (formed by alcoholysis of an oil and esterification of a polyalkylene glycol to produce a mixture of mono-, di- and tri-glycerides and mono- and di-esters; e.g., stearoyl macrogol-32 glycerides). Such pharmaceutical compositions are advantageously administered orally.

Pharmaceutical compositions of the present invention can comprise about 10 % to about 50 %, about 25 % to about 50 %, about 30 % to about 45 %, or about 30 % to about 35 % by weight of a co-crystal; about 10 % to about 50 %, about 25 % to about 50 %, about 30 % to about 45 %, or about 30 % to about 35 % by weight of an excipient which inhibits crystallization in aqueous solution, in simulated gastric fluid, or in simulated intestinal fluid; and about 5 % to about 50 %, about 10 % to about 40 %, about 15 % to about 35 %, or about 30 % to about 35 % by weight of a binding agent. In one example, the weight ratio of the co-crystal to the excipient which inhibits crystallization to binding agent is about 1 to 1 to 1.

Solid dosage forms of the invention can be prepared by any suitable process, not limited to processes described herein.

An illustrative process comprises (a) a step of blending an API of the invention with one or more excipients to form a blend, and (b) a step of tableting or encapsulating the blend to form tablets or capsules, respectively.

In a preferred process, solid dosage forms are prepared by a process comprising (a) a step of blending a co-crystal of the invention with one or more excipients to form a blend, (b) a step of granulating the blend to form a granulate, and (c) a step of tableting or

encapsulating the blend to form tablets or capsules respectively. Step (b) can be accomplished by any dry or wet granulation technique known in the art, but is preferably a dry granulation step. A salt of the present invention is advantageously granulated to form particles of about 1 micrometer to about 100 micrometer, about 5 micrometer to about 50 micrometer, or about 10 micrometer to about 25 micrometer. One or more diluents, one or more disintegrants and one or more binding agents are preferably added, for example in the blending step, a wetting agent can optionally be added, for example in the granulating step, and one or more disintegrants are preferably added after granulating but before tableting or encapsulating. A lubricant is preferably added before tableting. Blending and granulating can be performed independently under low or high shear. A process is preferably selected that forms a granulate that is uniform in API content, that readily disintegrates, that flows with sufficient ease so that weight variation can be reliably controlled during capsule filling or tableting, and that is dense enough in bulk so that a batch can be processed in the selected equipment and individual doses fit into the specified capsules or tablet dies.

In an alternative embodiment, solid dosage forms are prepared by a process that includes a spray drying step, wherein an API is suspended with one or more excipients in one or more sprayable liquids, preferably a non-protic (e.g., non-aqueous or non-alcoholic) sprayable liquid, and then is rapidly spray dried over a current of warm air. A granulate or spray dried powder resulting from any of the above illustrative processes can be compressed or molded to prepare tablets or encapsulated to prepare capsules. Conventional tableting and encapsulation techniques known in the art can be employed. Where coated tablets are desired, conventional coating techniques are suitable. Excipients for tablet compositions of the invention are preferably selected to provide a disintegration time of less than about 30 minutes, preferably about 25 minutes or less, more preferably about 20 minutes or less, and still more preferably about 15 minutes or less, in a standard disintegration assay.

Pharmaceutically acceptable co-crystals can be administered by controlled-, sustained-, or delayed-release means. Controlled-release pharmaceutical products have a common goal of improving drug therapy over that achieved by their non-controlled release counterparts. Ideally, the use of an optimally designed controlled-release

preparation in medical treatment is characterized by a minimum of drug substance being employed to cure or control the condition in a minimum amount of time. Advantages of controlled-release formulations include: 1) extended activity of the drug; 2) reduced dosage frequency; 3) increased patient compliance; 4) usage of less total drug; 5) reduction in local or systemic side effects; 6) minimization of drug accumulation; 7) reduction in blood level fluctuations; 8) improvement in efficacy of treatment; 9) reduction of potentiation or loss of drug activity; and 10) improvement in speed of control of diseases or conditions. (Kim, Cherng-ju, Controlled Release Dosage Form Design, 2 Technomic Publishing, Lancaster, Pa.: 2000).

Conventional dosage forms generally provide rapid or immediate drug release from the formulation. Depending on the pharmacology and pharmacokinetics of the drug, use of conventional dosage forms can lead to wide fluctuations in the concentrations of the drug in a patient's blood and other tissues. These fluctuations can impact a number of parameters, such as dose frequency, onset of action, duration of efficacy, maintenance of therapeutic blood levels, toxicity, side effects, and the like. Advantageously, controlled-release formulations can be used to control a drug's onset of action, duration of action, plasma levels within the therapeutic window, and peak blood levels. In particular, controlled- or extended-release dosage forms or formulations can be used to ensure that the maximum effectiveness of a drug is achieved while minimizing potential adverse effects and safety concerns, which can occur both from under dosing a drug (i.e., going below the minimum therapeutic levels) as well as exceeding the toxicity level for the drug.

Most controlled-release formulations are designed to initially release an amount of drug (active ingredient) that promptly produces the desired therapeutic effect, and gradually and continually release other amounts of drug to maintain this level of therapeutic or prophylactic effect over an extended period of time. In order to maintain this constant level of drug in the body, the drug must be released from the dosage form at a rate that will replace the amount of drug being metabolized and excreted from the body. Controlled-release of an active ingredient can be stimulated by various conditions including, but not limited to, pH, ionic strength, osmotic pressure, temperature, enzymes, water, and other physiological conditions or compounds.

A variety of known controlled- or extended-release dosage forms, formulations, and devices can be adapted for use with the co-crystals and compositions of the invention. Examples include, but are not limited to, those described in U.S. Pat. Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; 4,008,719; 5,674,533; 5,059,595; 5,591,767; 5,120,548; 5,073,543; 5,639,476; 5,354,556; 5,733,566; and 6,365,185 B1; each of which is incorporated herein by reference. These dosage forms can be used to provide slow or controlled-release of one or more active ingredients using, for example, hydroxypropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems (such as OROS® (Alza Corporation, Mountain View, Calif. USA)), multilayer coatings, microparticles, liposomes, or microspheres or a combination thereof to provide the desired release profile in varying proportions. Additionally, ion exchange materials can be used to prepare immobilized, adsorbed co-crystals and thus effect controlled delivery of the drug. Examples of specific anion exchangers include, but are not limited to, Duolite® A568 and Duolite® AP143 (Rohm & Haas, Spring House, PA. USA).

One embodiment of the invention encompasses a unit dosage form which comprises a pharmaceutically acceptable co-crystal, or a solvate, hydrate, dehydrate, anhydrous, or amorphous form thereof, and one or more pharmaceutically acceptable excipients or diluents, wherein the pharmaceutical composition or dosage form is formulated for controlled-release. Specific dosage forms utilize an osmotic drug delivery system.

A particular and well-known osmotic drug delivery system is referred to as OROS® (Alza Corporation, Mountain View, Calif. USA). This technology can readily be adapted for the delivery of compounds and compositions of the invention. Various aspects of the technology are disclosed in U.S. Pat. Nos. 6,375,978 B1; 6,368,626 B1; 6,342,249 B1; 6,333,050 B2; 6,287,295 B1; 6,283,953 B1; 6,270,787 B1; 6,245,357 B1; and 6,132,420; each of which is incorporated herein by reference. Specific adaptations of OROS® that can be used to administer compounds and compositions of the invention include, but are not limited to, the OROS® Push-Pull™, Delayed Push-Pull™, Multi-Layer Push-Pull™, and Push-Stick™ Systems, all of which are well known. See, e.g., http://www.alza.com. Additional OROS® systems that can be used for the controlled oral

delivery of compounds and compositions of the invention include OROS®-CT and L-OROS®. Id.; see also, Delivery Times, vol. II, issue II (Alza Corporation).

Conventional OROS® oral dosage forms are made by compressing a drug powder (e.g. co-crystal) into a hard tablet, coating the tablet with cellulose derivatives to form a semi-permeable membrane, and then drilling an orifice in the coating (e.g., with a laser). Kim, Cherng-ju, Controlled Release Dosage Form Design, 231-238 (Technomic Publishing, Lancaster, Pa.: 2000). The advantage of such dosage forms is that the delivery rate of the drug is not influenced by physiological or experimental conditions. Even a drug with a pH-dependent solubility can be delivered at a constant rate regardless of the pH of the delivery medium. But because these advantages are provided by a build-up of osmotic pressure within the dosage form after administration, conventional OROS® drug delivery systems cannot be used to effectively deliver drugs with low water solubility. Id. at 234. Because co-crystals of this invention can be far more soluble in water than the API itself, they are well suited for osmotic-based delivery to patients. This invention does, however, encompass the incorporation of conventional crystalline API (e.g. pure API without co-crystal former), and non-salt isomers and isomeric mixtures thereof, into OROS® dosage forms.

A specific dosage form of the invention comprises: a wall defining a cavity, the wall having an exit orifice formed or formable therein and at least a portion of the wall being semipermeable; an expandable layer located within the cavity remote from the exit orifice and in fluid communication with the semipermeable portion of the wall; a dry or substantially dry state drug layer located within the cavity adjacent to the exit orifice and in direct or indirect contacting relationship with the expandable layer; and a flow-promoting layer interposed between the inner surface of the wall and at least the external surface of the drug layer located within the cavity, wherein the drug layer comprises a co-crystal, or a solvate, hydrate, dehydrate, anhydrous, or amorphous form thereof. See U.S. Pat. No. 6,368,626, the entirety of which is incorporated herein by reference.

Another specific dosage form of the invention comprises: a wall defining a cavity, the wall having an exit orifice formed or formable therein and at least a portion of the wall being semipermeable; an expandable layer located within the cavity remote from the exit orifice and in fluid communication with the semipermeable portion of the wall; a

drug layer located within the cavity adjacent the exit orifice and in direct or indirect contacting relationship with the expandable layer; the drug layer comprising a liquid, active agent formulation absorbed in porous particles, the porous particles being adapted to resist compaction forces sufficient to form a compacted drug layer without significant exudation of the liquid, active agent formulation, the dosage form optionally having a placebo layer between the exit orifice and the drug layer, wherein the active agent formulation comprises a co-crystal, or a solvate, hydrate, dehydrate, anhydrous, or amorphous form thereof. See U.S. Pat. No. 6,342,249, the entirety of which is incorporated herein by reference.

The invention will now be described in further detail, by way of example, with reference to the accompanying drawings.

EXEMPLIFICATION

General Methods for the Preparation of Co-Crystals

a) High Throughput crystallization using the CrystalMax™ platform

CrystalMax™ comprises a sequence of automated, integrated high throughput robotic stations capable of rapid generation, identification and characterization of polymorphs, salts, and co-crystals of APIs and API candidates. Worksheet generation and combinatorial mixture design is carried out using proprietary design software Architect™. Typically, an API or an API candidate is dispensed from an organic solvent into tubes and dried under a stream of nitrogen. Salts and/or co-crystal formers may also be dispensed and dried in the same fashion. Water and organic solvents may be combinatorially dispensed into the tubes using a multi-channel dispenser. Each tube in a 96-tube array is then sealed within 15 seconds of combinatorial dispensing to avoid solvent evaporation. The mixtures are then rendered supersaturated by heating to 70 degrees C for 2 hours followed by a 1 degree C/minute cooling ramp to 5 degrees C. Optical checks are then conducted to detect crystals and/or solid material. Once a solid has been identified in a tube, it is isolated through aspiration and drying. Raman spectra

are then obtained on the solids and cluster classification of the spectral patterns is performed using proprietary software (Inquire™).

b) Crystallization from solution

Co-crystals may be obtained by dissolving the separate components in a solvent and adding one to the other. The co-crystal may then precipitate or crystallize as the solvent mixture is evaporated slowly. The co-crystal may also be obtained by dissolving the two components in the same solvent or a mixture of solvents.

c) Crystallization from the melt (Co-melting)

A co-crystal may be obtained by melting the two components together (i.e., co-melting) and allowing recrystallization to occur. In some cases, an anti-solvent may be added to facilitate crystallization.

d) Thermal microscopy

A co-crystal may be obtained by melting the higher melting component on a glass slide and allowing it to recrystallize. The second component is then melted and is also allowed to recrystallize. The co-crystal may form as a separated phase/band in between the eutectic bands of the two original components.

e) Mixing and/or grinding

A co-crystal may be obtained by mixing or grinding two components together in the solid state.

f) Co-sublimation

A co-crystal may be obtained by co-subliming a mixture of an API and a co-crystal former in the same sample cell as an intimate mixture either by heating, mixing or placing the mixture under vacuum. A co-crystal may also be obtained by co-sublimation using a Kneudsen apparatus where the API and the co-crystal former are contained in separate sample cells, connected to a single cold finger, each of the sample cells is

maintained at the same or different temperatures under a vaccum atmosphere in order to co-sublime the two components onto the cold-finger forming the desired co-crystal.

Analytical Methods

Procedure for DSC analysis

DSC analysis of the samples was performed using a Q1000 Differential Scanning Calorimeter (TA Instruments, New Castle, DE, U.S.A.), which uses Advantage for QW-Series, version 1.0.0.78, Thermal Advantage Release 2.0 (2001 TA Instruments-Water LLC). In addition, the analysis software used was Universal Analysis 2000 for Windows 95/95/2000/NT, version 3.1E;Build 3.1.0.40 (2001 TA Instruments-Water LLC).

For the DSC analysis, the purge gas used was dry nitrogen, the reference material was an empty aluminum pan that was crimped, and the sample purge was 50 mL/minute.

DSC analysis of the sample was performed by placing ≤ 2 mg of sample in an aluminum pan with a crimped pan closure. The starting temperature was typically 20 degrees C with a heating rate of 10 degrees C/minute, and the ending temperature was 300 degrees C. Unless otherwise indicated, all reported transitions are as stated +/- 1.0 degrees C.

Procedure for TGA analysis

TGA analysis of samples was performed using a Q500 Thermogravimetric Analyzer (TA Instruments, New Castle, DE, U.S.A.), which uses Advantage for QW-Series, version 1.0.0.78, Thermal Advantage Release 2.0 (2001 TA Instruments-Water LLC). In addition, the analysis software used was Universal Analysis 2000 for Windows 95/95/2000/NT, version 3.1E;Build 3.1.0.40 (2001 TA Instruments-Water LLC).

For all of the TGA experiments, the purge gas used was dry nitrogen, the balance purge was 40 mL/minute N_2, and the sample purge was 60 mL/minute N_2.

TGA of the sample was performed by placing ≤ 2 mg of sample in a platinum pan. The starting temperature was typically 20 degrees C with a heating rate of 10 degrees C/minute, and the ending temperature was 300 degrees C.

Procedure for PXRD analysis

A powder X-ray diffraction pattern for the samples was obtained using a D/Max Rapid, Contact (Rigaku/MSC, The Woodlands, TX, U.S.A.), which uses as its control software RINT Rapid Control software, Rigaku Rapid/XRD, version 1.0.0 (1999 Rigaku Co.). In addition, the analysis software used were RINT Rapid display software, version 1.18 (Rigaku/MSC), and JADE XRD Pattern Processing, versions 5.0 and 6.0 ((1995-2002, Materials Data, Inc.).

For the PXRD analysis, the acquisition parameters were as follows: source was Cu with a K line at 1.5406Å; x-y stage was manual; collimator size was 0.3 or 0.8 mm; capillary tube (Charles Supper Company, Natick, MA, U.S.A.) was 0.3 mm ID; reflection mode was used; the power to the X-ray tube was 46 kV; the current to the X-ray tube was 40 mA; the omega-axis was oscillating in a range of 0-5 degrees at a speed of 1 degree/minute; the phi-axis was spinning at an angle of 360 degrees at a speed of 2 degrees/second; 0.3 or 0.8 mm collimator; the collection time was 60 minutes; the temperature was room temperature; and the heater was not used. The sample was presented to the X-ray source in a boron rich glass capillary.

In addition, the analysis parameters were as follows: the integration 2-theta range was 2-40 or 60 degrees; the integration chi range was 0-360 degrees; the number of chi segments was 1; the step size used was 0.02; the integration utility was cylint; normalization was used; dark counts were 8; omega offset was 180; and chi and phi offsets were 0.

The relative intensity of peaks in a diffractogram is not necessarily a limitation of the PXRD pattern because peak intensity can vary from sample to sample, e.g., due to crystalline impurities. Further, the angles of each peak can vary by about +/- 0.1 degrees, preferably +/-0.05. The entire pattern or most of the pattern peaks may also shift by about +/- 0.1 degree due to differences in calibration, settings, and other variations from instrument to instrument and from operator to operator.

Procedure for Raman Acquisition, Filtering and Binning

Acquisition

The sample was either left in the glass vial in which it was processed or an aliquot of the sample was transferred to a glass slide. The glass vial or slide was positioned in the sample chamber. The measurement was made using an Almega™ Dispersive Raman (Almega™ Dispersive Raman, Thermo-Nicolet, 5225 Verona Road, Madison, WI 53711-4495) system fitted with a 785nm laser source. The sample was manually brought into focus using the microscope portion of the apparatus with a 10x power objective (unless otherwise noted), thus directing the laser onto the surface of the sample. The spectrum was acquired using the parameters outlined in Table XXII. (Exposure times and number of exposures may vary; changes to parameters will be indicated for each acquisition.)

Filtering and Binning

Each spectrum in a set was filtered using a matched filter of feature size 25 to remove background signals, including glass contributions and sample fluorescence. This is particularly important as large background signal or fluorescence limit the ability to accurately pick and assign peak positions in the subsequent steps of the binning process. Filtered spectra were binned using the peak pick and bin algorithm with the parameters given in Table XXIII. The sorted cluster diagrams for each sample set and the corresponding cluster assignments for each spectral file were used to identify groups of samples with similar spectra, which was used to identify samples for secondary analyses.

Table XXII. Raman Spectral acquisition parameters

Parameter	Setting Used
Exposure time (s)	2.0
Number of exposures	10
Laser source wavelength (nm)	785
Laser power (%)	100
Aperture shape	pin hole
Aperture size (um)	100
Spectral range	104-3428
Grating position	Single
Temperature at acquisition (degrees C)	24.0

Table XXIII. Raman Filtering and Binning Parameters

Parameter	Setting Used
Filtering Parameters	
Filter type	Matched
Filter size	25
QC Parameters	
Peak Height Threshold	1000
Region for noise test (cm^{-1})	0-10000
RMS noise threshold	10000
Automatically eliminate failed spectra	Yes
Region of Interest	
Include (cm^{-1})	104-3428
Exclude region I (cm^{-1})	
Exclude region II (cm^{-1})	
Exclude region III (cm^{-1})	
Exclude region IV (cm^{-1})	
Peak Pick Parameters	
Peak Pick Sensitivity	Variable
Peak Pick Threshold	100
Peak Comparison Parameters	
Peak Window (cm^{-1})	2
Analysis Parameters	
Number of clusters	Variable

Procedure for Single Crystal X-Ray Diffraction

Single crystal x-ray data were collected on a Bruker SMART-APEX CCD diffractometer (M. J. Zaworotko, Department of Chemistry, University of South Florida). Lattice parameters were determined from least squares analysis. Reflection data was

integrated using the program SAINT. The structure was solved by direct methods and refined by full matrix least squares using the program SHELXTL (Sheldrick, G. M. SHELXTL, Release 5.03; Siemans Analytical X-ray Instruments Inc.: Madison, WI).

The co-crystals of the present invention can be characterized, e.g., by the TGA or DSC data or by any one, any two, any three, any four, any five, any six, any seven, any eight, any nine, any ten, or any single integer number of PXRD 2-theta angle peaks or Raman shift peaks listed herein or disclosed in a figure, or by single crystal x-ray diffraction data.

Example 1

1:1 celecoxib:nicotinamide co-crystals were prepared. Celecoxib (100 mg, 0.26 mmol) and nicotinamide (32.0 mg, 0.26 mmol) were each dissolved in acetone (2 mL). The two solutions were mixed and the resulting mixture was allowed to evaporate slowly overnight. The precipitated solid was redissolved in acetone a second time and left to evaporate to dryness. The powder was collected and characterized. Detailed characterization of the celecoxib:nicotinamide co-crystal is listed in Table XXIV. Fig. 1A shows the PXRD diffractogram after subtraction of background noise. Fig. 1B shows the raw PXRD data. Fig. 2 shows a DSC thermogram of the celecoxib:nicotinamide co-crystal. Fig. 3 shows a TGA thermogram of the celecoxib:nicotinamide co-crystal. Fig. 4 shows a Raman spectrum of the celecoxib:nicotinamide co-crystal.

Example 2

Co-crystals of celecoxib and 18-crown-6 were prepared. A solution of celecoxib (157.8 mg, 0.4138 mmol) in Et_2O (10.0 mL) was added to 18-crown-6 (118.1 mg, 0.447 mmol). The opaque solid dissolves immediately and a white solid subsequently began to crystallize very rapidly. The solid was collected via filtration and was washed with additional diethyl ether (5 mL). Detailed characterization of the celecoxib:18-crown-6 co-crystal is listed in Table XXIV. Fig. 5A shows the PXRD diffractogram after subtraction of background noise. Fig. 5B shows the raw PXRD data. Fig. 6 shows a

DSC thermogram of the celecoxib:18-crown-6 co-crystal. Fig. 7 shows a TGA thermogram of the celecoxib:18-crown-6 co-crystal.

Example 3

Co-crystals of topiramate and 18-crown-6 were prepared. To topiramate (100 mg, 0.29 mmol) dissolved in diethyl ether (5 mL) was added 18-crown-6 (78 mg, 0.29 mmol) in diethyl ether (5 mL). Upon addition of 18-crown-6, the solution became cloudy and was sonicated for 30 seconds. The solution was left standing for 1 hour and a colorless precipitate was observed. The precipitate was collected, washed with diethyl ether and dried to give a 1:1 co-crystal of topiramate:18-crown-6 as a colorless solid. Detailed characterization of the co-crystal is listed in Table XXIV. Fig. 8A shows the PXRD diffractogram after subtraction of background noise. Fig. 8B shows the raw PXRD data. Fig. 9 shows a DSC thermogram of the topiramate:18-crown-6 co-crystal.

Example 4

Co-crystals of olanzapine and nicotinamide (Forms I, II and III) were prepared. A 9-block experiment was designed with 12 solvents. (A block is a receiving plate, which can be, for example, an industry standard 24 well, 96 well, 384 well, or 1536 well format, or a custom format.) 864 crystallization experiments with 10 co-crystal formers and 3 concentrations were carried out using the CrystalMax™ platform. Form I was obtained from mixtures containing 1:1 and 1:2 molar ratios of olanzapine:nicotinamide in 1,2-dichloroethane. Form II was obtained from mixtures containing a 1:2 molar ratio of olanzapine and nicotinamide in isopropyl acetate. PXRD and DSC characterization of the olanzapine:nicotinamide co-crystals are listed in Table XXIV. Fig. 10A shows the PXRD diffractogram of form I after subtraction of background noise. Fig. 10B shows the raw PXRD data of form I. Fig. 11 shows a DSC thermogram of the olanzapine:nicotinamide form I co-crystal. Fig. 12 shows the PXRD diffractogram of olanzapine:nicotinamide form II after subtraction of background noise.

Co-crystals of olanzapine and nicotinamide (Form III) were prepared. Olanzapine (40 microliters of 25 mg/mL stock solution in tetrahydrofuran) and nicotinamide (37.6 microliters of 20 mg/mL stock solution in methanol) were added to a glass vial and dried under a flow of nitrogen. To the solid mixture was added isopropyl acetate (100 microliters) and the vial was sealed with an aluminum cap. The suspension was then heated at 70 degrees C for two hours in order to dissolve all of the solid material. The solution was then cooled to 5 degrees C and maintained at that temperature for 24 hours. After 24 hours the vial was uncapped and the mixture was concentrated to 50 microliters of total volume. The vial was then resealed with an aluminum cap and was maintained at 5 degrees C for an additional 24 hours. Large, yellow plates were observed and were collected (Form III). The solid was characterized with single crystal x-ray diffraction and powder x-ray diffraction. PXRD characterization of the co-crystal is listed in Table XXIV. Fig. 13A shows the PXRD diffractogram of form III after subtraction of background noise. Fig. 13B shows the raw PXRD data of form III. Figs. 14A-D show packing diagrams of the olanzapine:nicotinamide form III co-crystal.

Single crystal x-ray analysis reveals that the olanzapine:nicotinamide (Form III) co-crystal is made up of a ternary system containing olanzapine, nicotinamide, water and isopropyl acetate in the unit cell. The co-crystal crystallizes in the monoclinic space group $P2_1/c$ and contains two olanzapine molecules, one nicotinamide molecule, 4 water molecules and one isopropyl acetate molecule in the asymmetric unit. The packing diagram is made up of a two-dimensional hydrogen-bonded network with the water molecules connecting the olanzapine and nicotinamide moieties. The packing diagram is also comprised of alternating olanzapine and nicotinamide layers connected through hydrogen bonding via the water and isopropyl acetate molecules, as shown in Figure 14B. The olanzapine layer propagates along the b axis at c/4 and 3c/4. The nicotinamide layer propagates along the b axis at c/2. The top of Figure 14C illustrates the nicotinamide superstructure. The nicotinamide molecules form dimers which hydrogen bond to chains of 4 water molecules. The water chains terminate with isopropyl acetate molecules on each side.

Crystal data: $C_{45}H_{64}N_{10}O_7S_2$, M = 921.18, monoclinic P21/c; a = 14.0961(12) Å, b = 12.5934(10) Å, c = 27.219(2) Å, $\alpha = 90°$, $\beta = 97.396(2)°$, $\gamma = 90°$, T = 100(2) K, Z =

4, $D_c = 1.276$ Mg/m^3,U = 4793.6(7) Å^3, $\lambda = 0.71073$ Å; 24952 reflections measured, 8457 unique ($R_{int} = 0.0882$). Final residuals were $R_1 = 0.0676$, $wR_2 = 0.1461$ for $I>2\sigma(I)$, and $R_1 = 0.1187$, $wR_2 = 0.1687$ for all 8457 data.

Example 5

A co-crystal of *cis*-itraconazole and succinic acid was prepared. To a solution of succinic acid (16.8 mg, 0.142 mmol) in tetrahydrofuran (THF) (0.50 mL) was added *cis*-itraconazole (100 mg, 0.142 mmol). A clear solution formed with heating (60 degrees C) and stirring. Upon cooling to room temperature (25 degrees C), crystals began to form. The solid was collected by filtration and washed with cold THF (2 mL). The white solid was air-dried and placed in a glass vial. The crystalline substance was found to be a succinic acid co-crystal of *cis*-itraconazole. The solid was characterized by PXRD and DSC. Fig. 15 shows the PXRD diffractogram after subtraction of background noise. Fig. 16 shows a DSC thermogram of the co-crystal.

Example 6

A co-crystal of *cis*-itraconazole and fumaric acid was prepared. To a blend of fumaric acid (8.40 mg, 0.072 mmol) and *cis*-itraconazole (51.8 mg, 0.073 mmol) was added tetrahydrofuran (THF) (1.0 mL). A clear solution formed with heating (60 degrees C) and stirring. Upon cooling to room temperature (25 degrees C), no crystals formed. To the clear solution was added t-butyl methyl ether (1.0 mL). A white solid formed immediately and was collected by filtration and washed with cold t-butyl methyl ether (2 mL). The white solid was air-dried and placed in a glass vial. The crystalline substance was found to be a fumaric acid co-crystal of *cis*-itraconazole. The solid was characterized by PXRD and DSC. Fig. 17 shows the PXRD diffractogram after subtraction of background noise. Fig. 18 shows a DSC thermogram of the co-crystal.

Example 7

A co-crystal of *cis*-itraconazole and L-tartaric acid was prepared. To a solution of L-tartaric acid (21.3 mg, 0.142 mmol) in tetrahydrofuran (THF) (0.50 mL) was added *cis*-itraconazole (100 mg, 0.142 mmol). A clear solution formed with heating (60 degrees C) and stirring. Upon cooling to room temperature (25 degrees C), crystals began to form. The solid was collected by filtration and washed with cold THF (2 mL). The white solid was air-dried and placed in a glass vial. The crystalline substance was found to be an L-tartaric acid co-crystal of *cis*-itraconazole. The solid was characterized by PXRD and DSC. Fig. 19 shows the PXRD diffractogram after subtraction of background noise. Fig. 20 shows a DSC thermogram of the co-crystal.

Example 8

A co-crystal of *cis*-itraconazole and L-malic acid was prepared. To a solution of L-malic acid (19.1 mg, 0.143 mmol) in tetrahydrofuran (THF) (0.50 mL) was added *cis*-itraconazole (100 mg, 0.142 mmol). A clear solution formed with heating (60 degrees C) and stirring. Upon cooling to room temperature (25 degrees C), crystals began to form. The solid was collected by filtration and washed with cold THF (2 mL). The white solid was air-dried and placed in a glass vial. The crystalline substance was found to be an L-malic acid co-crystal of *cis*-itraconazole. The solid was characterized by PXRD and DSC. Fig. 21 shows the PXRD diffractogram after subtraction of background noise. Fig. 22 shows a DSC thermogram of the co-crystal.

Example 9

A co-crystal of *cis*-itraconazole hydrochloride and DL-tartaric acid was prepared. To a suspension of *cis*-itraconazole freebase (20.1 g, 0.0285 mol) in absolute ethanol (100 mL) was added a solution of hydrochloric acid (1.56 g, 0.0428 mol) and DL-tartaric acid (2.99 g, 0.0171mol) in absolute ethanol (100 mL). A clear solution formed with stirring and heating to reflux. The hot solution was gravity filtered and allowed to cool to room temperature (25 degrees C). Upon cooling white crystals formed. The solid was

collected by filtration and washed with cold absolute ethanol (15 mL). The white solid was dried in a vacuum oven overnight at 80 degrees C. The crystalline substance was found to be a DL-tartaric acid co-crystal of *cis*-itraconazole hydrochloride. The solid was characterized by PXRD and DSC. Fig. 23 shows the PXRD diffractogram after subtraction of background noise. Fig. 24 shows a DSC thermogram of the co-crystal.

Example 10

Co-crystals of modafinil and malonic acid were prepared. Using a 250 mg/ml modafinil-acetic acid solution, malonic acid was dissolved on a hotplate (about 67 degrees C) at a 1:2 modafinil to malonic acid ratio. The mixture was dried under flowing nitrogen overnight. A powdery white solid was produced. After further drying for 1 day, acetic acid was removed (as determined by TGA) and the crystal structure of the modafinil:malonic acid (Form I) co-crystal, as determined by PXRD, remained the same. The modafinil:malonic acid (Form I) co-crystal was also prepared by grinding the API and co-crystal former together. 2.50 g of modafinil was mixed with 1.01 g of malonic acid in a large mortar and pestle (malonic acid added in increments over 7 days with about a 1:1.05 ratio made on the first day and increments added over the next seven days which resulted in a 1:2 modafinil:malonic acid ratio). The mixture was ground for 45 minutes initially and 20 minutes each time more malonic acid was added. On the seventh day the mixture of co-crystal and starting components was heated in a sealed 20 mL vial at 80 degrees C for about 35 minutes to facilitate completion of the co-crystal formation. PXRD analysis of the resultant material was completed and the diffractogram is shown in Fig. 25, after subtraction of background noise. Fig. 26 shows a DSC thermogram of the modafinil:malonic acid Form I co-crystal. Fig. 27 shows the Raman spectrum of the modafinil:malonic acid Form I co-crystal. Fig. 27 comprises peaks, in order of decreasing intensity, of 1004, 222, 633, 265, 1032, 1183, 814, 1601, 490, 718, 767, 361, 917, 1104, 889, 412, 1225, 1251, 1398, 1442, 1731, 1298, 3065, and 2949 cm^{-1}. Single crystal data of the modafinil:malonic acid Form I co-crystal were acquired and are reported below.

Crystal data: $C_{18}H_{19}NO_6S$, M = 377.40, monoclinic C2/c; a = 18.728(8) angstroms, b = 5.480(2) angstroms, c = 33.894(13) angstroms, alpha = 90 degrees, beta = 91.864(9) degrees, gamma = 90 degrees, T = 100(2) K, Z = 8, D_c = 1.442 Mg/m^3, U = 3477(2) cubic angstroms, λ = 0.71073 angstroms, 6475 reflections measured, 3307 unique (R_{int} = 0.1567). Final residuals were R_1 = 0.1598, wR_2 = 0.3301 for I>2sigma(I), and R_1 = 0.2544, wR_2 = 0.3740 for all 3307 data.

A polymorph of the modafinil:malonic acid Form I co-crystal was prepared in a vial. 11.4 mg of modafinil and 8.9 mg of malonic acid were dissolved in 2 mL of acetone. The solids dissolved at room temperature, and the vial was left open to evaporate the solvent in air. Large parallelogram shaped crystals formed on the walls and bottom of the vial. The PXRD diffractogram of the large crystals showed modafinil:malonic acid co-crystals Form II, a polymorphic form of modafinil:malonic acid Form I. Fig. 28 shows the PXRD diffractogram of the modafinil:malonic acid Form II co-crystal after subtraction of background noise.

Example 11

Co-crystals of modafinil and glycolic acid were prepared. Modafinil (1 mg, 0.0037mmol) and glycolic acid (0.30 mg, 0.0037 mmol) were dissolved in acetone (400 microliters). The solution was allowed to evaporate to dryness and the resulting solid was characterized using PXRD. PXRD data for the modafinil:glycolic acid co-crystal is listed in Table XXIV. Fig. 29A shows the PXRD diffractogram after subtraction of background noise. Fig. 29B shows the raw PXRD data.

Example 12

Co-crystals of modafinil and maleic acid were prepared. Using a 250 mg/ml modafinil-acetic acid solution, maleic acid was dissolved on a hotplate (about 67 degrees C) at a 2:1 modafinil to maleic ratio. The mixture was dried under flowing nitrogen overnight. A clear amorphous material remained. Solids began to grow after 2 days stored in a sealed vial at room temperature. The solid was collected and characterized as

the modafinil:maleic acid co-crystal using PXRD. Fig. 30A shows the PXRD diffraetogram after subtraction of background noise. Fig. 30B shows the raw PXRD data.

Example 13

Co-crystals of 5-fluorouracil and urea were prepared. To 5-fluorouracil (1g, 7.69 mmol) and urea (0.46g, 7.69 mmol) was added methanol (100 mL). The solution was heated at 65 degrees C and sonicated until all the material dissolved. The solution was then cooled to 5 degrees C and maintained at that temperature overnight. After about 3 days a white precipitate was observed and collected. The solid was characterized by DSC, PXRD, Raman spectroscopy, and TGA as the 5-fluorouracil:urea co-crystal. Characterization data are listed in Table XXIV. Fig. 31A shows the PXRD diffractogram after subtraction of background noise. Fig. 31B shows the raw PXRD data. Fig. 32 shows a DSC thermogram of the 5-fluorouracil:urea co-crystal. Fig. 33 shows a TGA thermogram of the 5-fluorouracil:urea co-crystal. Fig. 34 shows a Raman spectrum of the 5-fluorouracil:urea co-crystal. Single crystal data of the 5-fluorouracil:urea co-crystal were acquired and are reported below.

Crystal data: $C_5H_7FN_4O_3$, M = 190.15, monoclinic C2/C, a = 9.461(3) angstroms, b = 10.487(3) angstroms, c = 15.808(4) angstroms, alpha = 90 degrees, beta = 99.891(5), gamma = 90 degrees, T = 100(2) K, Z = 8, D_c = 1.635 Mg/m^3, U = 1545.2(7) cubic angstroms, λ = 0.71073 angstroms, 3419 reflections measured, 1633 unique (R_{int} = 0.0330). Final residuals were R_1 = 0.0667, wR_2 = 0.1505 for I>2sigma(I), and R_1 = 0.0872, wR_2 = 0.1598 for all 1633 data.

Example 14

Co-crystals of hydrochlorothiazide and nicotinic acid were prepared. Hydrochlorothiazide (12.2 mg, 0.041 mmol) and nicotinic acid (5 mg, 0.041 mmol) were dissolved in methanol (1 mL). The solution was then cooled to 5 degrees C and maintained at that temperature for 12 hours. A white solid precipitated and was collected and characterized as the hydrochlorothiazide:nicotinic acid co-crystal using PXRD. Fig.

35A shows the PXRD diffractogram after subtraction of background noise. Fig. 35B shows the raw PXRD data.

Example 15

Co-crystals of hydrochlorothiazide and 18-crown-6 were prepared. Hydrochlorothiazide (100 mg, 0.33 mmol) was dissolved in diethyl ether (15 mL) and was added to a solution of 18-crown-6 (87.2 mg, 0.33 mmol) in diethyl ether (15 mL). A white precipitate immediately began to form and was collected and characterized as the hydrochlorothiazide:18-crown-6 co-crystal using PXRD. Fig. 36A shows the PXRD diffractogram after subtraction of background noise. Fig. 36B shows the raw PXRD data.

Example 16

Co-crystals of hydrochlorothiazide and piperazine were prepared. Hydrochlorothiazide (17.3 mg, 0.058 mmol) and piperazine (5 mg, 0.058 mmol) were dissolved in a 1:1 mixture of ethyl acetate and acetonitrile (1 mL). The solution was then cooled to 5 degrees C and maintained at that temperature for 12 hours. A white solid precipitated and was collected and characterized as the hydrochlorothiazide:piperazine co-crystal using PXRD. Fig. 37A shows the PXRD diffractogram after subtraction of background noise. Fig. 37B shows the raw PXRD data.

Example 17

Acetaminophen:4,4'-bipyridine:water (1:1:1 stoichiometry)

50 mg (0.3307 mmol) acetaminophen and 52 mg (0.3329 mmol) 4,4'-bipyridine were dissolved in hot water and allowed to stand. Slow evaporation yielded colorless needles of a 1:1:1 acetaminophen:4,4'-bipyridine:water co-crystal, as shown in Figs. 38A-B.

Crystal data: (Bruker SMART-APEX CCD Diffractometer). triclinic, space group $P\bar{1}$; a = 7.0534(8), b = 9.5955(12), c = 19.3649(2) Å, α = 86.326(2), β = 80.291(2),

$\gamma = 88.880(2)°$, $U = 1308.1(3)$ Å^3, T = 200(2) K, Z = 2, μ(Mo-Kα) = 0.090 mm^{-1}, $D_c = 1.294$ Mg/m^3, $\lambda = 0.71073$ Å, F(000) = 537, $2\theta_{max} = 25.02°$; 6289 reflections measured, 4481 unique ($R_{int} = 0.0261$). Final residuals for 344 parameters were $R_1 = 0.0751$, $wR_2 = 0.2082$ for $I>2\sigma(I)$, and $R_1 = 0.1119$, $wR_2 = 0.2377$ for all 4481data.

Crystal packing: The co-crystals contain bilayered sheets in which water molecules act as a hydrogen bonded bridge between the network bipyridine moieties and the acetaminophen. Bipyridine guests are sustained by π-π stacking interactions between two network bipyridines. The layers stack via π-π interactions between the phenyl groups of the acetaminophen moieties.

Differential Scanning Calorimetry: (TA Instruments 2920 DSC), 57.77 degrees C (endotherm); m.p. = 58-60 degrees C (MEL-TEMP); (acetaminophen m.p. = 169 degrees C, 4,4'-bipyridine m.p. = 111-114 degrees C).

Example 18

Phenytoin:Pyridone (1:1 stoichiometry)

28 mg (0.1109 mmol) phenytoin and 11 mg (0.1156 mmol) 4-hydroxypyridone were dissolved in 2 mL acetone and 1 mL ethanol with heating and stirring. Slow evaporation yielded colorless needles of a 1:1 phenytoin:pyridone co-crystal, as shown in Figs. 39A-B.

Crystal data: (Bruker SMART-APEX CCD Diffractometer), $C_{20}H_{17}N_3O_3$, M = 347.37, monoclinic $P2_1/c$; a = 16.6583(19), b = 8.8478(10), c = 11.9546(14) Å, $\beta = 96.618(2)°$, $U = 1750.2(3)$ Å^3, T = 200(2) K, Z = 4, μ(Mo-Kα) = 0.091 mm^{-1}, $D_c = 1.318$ Mg/m^3, $\lambda = 0.71073$ Å, F(000) = 728, $2\theta_{max} = 56.60°$; 10605 reflections measured, 4154 unique ($R_{int} = 0.0313$). Final residuals for 247 parameters were $R_1 = 0.0560$, $wR_2 = 0.1356$ for $I>2\sigma(I)$, and $R_1 = 0.0816$, $wR_2 = 0.1559$ for all 4154 data.

Crystal packing: The co-crystal is sustained by hydrogen bonding of adjacent phentoin molecules between the carbonyl and the amine closest to the tetrahedral carbon, and by hydrogen bonding between pyridone carbonyl functionalities and the amine not involved in phenytoin-phenytoin interactions. The pyridone carbonyl also hydrogen bonds with adjacent pyridone molecules forming a one-dimensional network.

Infrared Spectroscopy: (Nicolet Avatar 320 FTIR), characteristic peaks for the co-crystal were identified as: 2° amine found at 3311cm^{-1}, carbonyl (ketone) found at 1711cm^{-1}, olephin peak found at 1390cm^{-1}.

Differential Scanning Calorimetry: (TA Instruments 2920 DSC), 233.39 degrees C (endotherm) and 271.33 degrees C (endotherm); m.p. = 231-233 degrees C (MEL-TEMP); (phenytoin m.p. = 295 degrees C, pyridone m.p. = 148 degrees C).

Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA), a 29.09% weight loss starting at 192.80 degrees C, 48.72% weight loss starting at 238.27 degrees C, and 18.38% loss starting at 260.17 degrees C followed by complete decomposition.

Powder x-ray diffraction: (Rigaku Miniflex Diffractometer using Cu Kα (λ = 1.540562), 30kV, 15mA). The powder data were collected over an angular range of 3° to 40° 2θ in continuous scan mode using a step size of 0.02° 2θ and a scan speed of 2.0°/minute. PXRD: Showed analogous peaks to the simulated PXRD derived from the single crystal data. experimental (calculated): 5.2 (5.3); 11.1 (11.3); 15.1 (15.2); 16.2 (16.4); 16.7 (17.0); 17.8 (17.9); 19.4 (19.4); 19.8 (19.7); 20.3 (20.1); 21.2 (21.4); 23.3 (23.7); 26.1 (26.4); 26.4 (26.6); 27.3 (27.6); 29.5 (29.9).

Example 19

Aspirin (acetylsalicylic acid):4,4'-bipyridine (2:1 stoichiometry)

50 mg (0.2775 mmol) aspirin and 22 mg (0.1388 mmol) 4,4'-bipyridine were dissolved in 4 mL hexane. 8 mL ether was added to the solution and allowed to stand for one hour, yielding colorless needles of a 2:1 aspirin:4,4'-bipyridine co-crystal, as shown in Figs. 40A-D. Alternatively, aspirin:4,4'-bipyridine (2:1 stoichiometry) can be made by grinding the solid ingredients in a pestle and mortar.

Crystal data: (Bruker SMART-APEX CCD Diffractometer), $C_{28}H_{24}N_2O_8$, M = 516.49, orthorhombic *Pbcn*; a = 28.831(3), b = 11.3861(12), c = 8.4144(9) Å, U = 2762.2(5) Å^3, T = 173(2) K, Z = 4, μ(Mo-Kα) = 0.092 mm^{-1}, D_c = 1.242 Mg/m^3, λ = 0.71073 Å, F(000) = 1080, $2\theta_{max}$ = 25.02°; 12431 reflections measured, 2433 unique

(R_{int} = 0.0419). Final residuals for 202 parameters were R_1 = 0.0419, wR_2 = 0.1358 for I>2σ(I), and R_1 = 0.0541, wR_2 = 0.1482 for all 2433 data.

Crystal packing: The co-crystal contains the carboxylic acid-pyridine heterodimer that crystallizes in the *Pbcn* space group. The structure is an inclusion compound containing disordered solvent in the channels. In addition to the dominant hydrogen bonding interaction of the heterodimer, π-π stacking of the bipyridine and phenyl groups of the aspirin and hydrophobic interactions contribute to the overall packing interactions.

Infrared Spectroscopy: (Nicolet Avatar 320 FTIR), characteristic (-COOH) peak at 1679 cm^{-1} was shifted up and less intense at 1694cm^{-1}, where as the lactone peak is shifted down slightly from 1750cm^{-1} to 1744cm^{-1}.

Differential Scanning Calorimetry: (TA Instruments 2920 DSC), 95.14 degrees C (endotherm); m.p. = 91-96 degrees C (MEL-TEMP); (aspirin m.p. = 1345 degrees C, 4,4'-bipyridine m.p. = 111-114 degrees C).

Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA), weight loss of 9% starting at 22.62 degrees C, 49.06% weight loss starting at 102.97 degrees C followed by complete decomposition starting at 209.37 degrees C.

Example 20

Ibuprofen:4,4'-Bipyridine (2:1 stoichiometry)

50 mg (0.242 mmol) racemic ibuprofen and 18mg (0.0960 mmol) 4,4'-bipyridine were dissolved in 5 mL acetone. Slow evaporation of the solvent yielded colorless needles of a 2:1 ibuprofen:4,4'-bipyridine co-crystal, as shown in Figs. 41A-D.

Crystal data: (Bruker SMART-APEX CCD Diffractometer), $C_{36}H_{44}N_2O_4$, M = 568.73, triclinic, space group *P-1*; a = 5.759(3), b = 11.683(6), c = 24.705(11) Å, α = 93.674(11), β = 90.880(10), γ = 104.045(7)°, *U* = 1608.3(13) $Å^3$, T= 200(2) K, Z = 2, μ(Mo-Kα) = 0.076 mm^{-1}, D_c = 1.174 Mg/m^3, λ = 0.71073 Å, F(000) = 612, $2\theta_{max}$ = 23.29°; 5208 reflections measured, 3362 unique (R_{int} = 0.0826). Final residuals for 399 parameters were R_1 = 0.0964, wR_2 = 0.2510 for I>2σ(I), and R_1 = 0.1775, wR_2 = 0.2987 for all 3362 data.

Crystal packing: The co-crystal contains ibuprofen:bipyridine heterodimers, sustained by two hydrogen bonded carboxylic acidpyridine supramolecular synthons, arranged in a herringbone motif that packs in the space group *P-1*. The heterodimer is an extended version of the homodimer and packs to form a two-dimensional network sustained by π-π stacking of the bipyridine and phenyl groups of the ibuprofen and hydrophobic interactions from the ibuprofen tails.

Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). Analysis observed stretching of aromatic C-H at 2899 cm^{-1}; N--H bending and scissoring at 1886 cm_{-1}; C=O stretching at 1679 cm^{-1}; C-H out-of-plane bending for both 4,4'-bipyridine and ibuprofen at 808 cm^{-1} and 628 cm^{-1}.

Differential Scanning Calorimetry: (TA Instruments 2920 DSC), 64.85 degrees C (endotherm) and 118.79 degrees C (endotherm); m.p. = 113-120 degrees C (MEL-TEMP); (ibuprofen m.p. = 75-77 degrees C, 4,4'-bipyridine m.p. = 111-114 degrees C).

Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA), 13.28% weight loss between room temperature and 100.02 degrees C immediately followed by complete decomposition.

Powder x-ray diffraction: (Rigaku Miniflex Diffractometer using Cu Kα (λ = 1.540562), 30kV, 15mA). The powder data were collected over an angular range of 3° to 40° 2θ in continuous scan mode using a step size of 0.02° 2θ and a scan speed of 2.0°/minute. PXRD derived from the single crystal data, experimental (calculated): 3.4 (3.6); 6.9 (7.2); 10.4 (10.8); 17.3 (17.5); 19.1 (19.7).

Example 21

Flurbiprofen:4,4'-bipyridine (2:1 stoichiometry)

50 mg (0.2046 mmol) flurbiprofen and 15 mg (0.0960 mmol) 4,4'-bipyridine were dissolved in 3 mL acetone. Slow evaporation of the solvent yielded colorless needles of a 2:1 flurbiprofen:4,4'-bipyridine co-crystal, as shown in Figs. 42A-D.

Crystal data: (Bruker SMART-APEX CCD Diffractometer), $C_{40}H_{34}F_2N_2O_4$, M = 644.69, monoclinic *P2$_1$/n*; a = 5.860(4), b = 47.49(3), c = 5.928(4) Å, β = 107.382 (8)°, *U* = 1574.3(19) $Å^3$, T = 200(2) K, Z = 2, μ(Mo-Kα) = 0.096 mm^{-1}, D_c = 1.360

Mg/m^3, $\lambda = 0.71073$ Å, F(000) = 676, $2\theta_{max} = 21.69°$; 4246 reflections measured, 1634 unique ($R_{int} = 0.0677$). Final residuals for 226 parameters were $R_1 = 0.0908$, $wR_2 = 0.2065$ for $I>2\sigma(I)$, and $R_1 = 0.1084$, $wR_2 = 0.2209$ for all 1634 data.

Crystal packing: The co-crystal contains flurbiprofen:bipyridine heterodimers, sustained by two hydrogen bonded carboxylic acidpyridine supramolecular synthon, arranged in a herringbone motif that packs in the space group *P2₁/n*. The heterodimer is an extended version of the homodimer and packs to form a two-dimensional network sustained by π-π stacking and hydrophobic interactions of the bipyridine and phenyl groups of the flurbiprofen.

Infrared Spectroscopy: (Nicolet Avatar 320 FTIR), aromatic C-H stretching at 3057 cm^{-1} and 2981 cm^{-1}; N--H bending and scissoring at 1886 cm^{-1}; C=O stretching at 1690 cm^{-1}; C=C and C=N ring stretching at 1418 cm^{-1}.

Differential Scanning Calorimetry: (TA Instruments 2920 DSC), 162.47 degrees C (endotherm); m.p. = 155-160 degrees C (MEL-TEMP); (flurbiprofen m.p. = 110-111 degrees C, 4,4'-bipyridine m.p. = 111-114 degrees C).

Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA), 30.93% weight loss starting at 31.13 degrees C and a 46.26% weight loss starting at 168.74 degrees C followed by complete decomposition.

Powder x-ray diffraction: (Rigaku Miniflex Diffractometer using Cu Kα ($\lambda = 1.540562$), 30kV, 15mA), the powder data were collected over an angular range of 3° to 40° 2θ in continuous scan mode using a step size of 0.02° 2θ and a scan speed of 2.0°/minute. PXRD derived from the single crystal data: experimental (calculated): 16.8 (16.8); 17.1 (17.5); 18.1 (18.4); 19.0 (19.0); 20.0 (20.4); 21.3 (21.7); 22.7 (23.0); 25.0 (25.6); 26.0 (26.1); 26.0 (26.6); 26.1 (27.5); 28.2 (28.7); 29.1 (29.7).

Example 22

Flurbiprofen:trans-1,2-bis (4-pyridyl) ethylene (2:1 stoichiometry)

25 mg (0.1023 mmol) flurbiprofen and 10 mg (0.0548 mmol) trans-1, 2-bis (4-pyridyl) ethylene were dissolved in 3 mL acetone. Slow evaporation of the solvent

yielded colorless needles of a 2:1 flurbiprofen:1,2-bis (4-pyridyl) ethylene co-crystal, as shown in Figs. 43A-B.

Crystal data: (Bruker SMART-APEX CCD Diffractometer), $C_{42}H_{36}F_2N_2O_4$, $M = 670.73$, monoclinic $P2_1/n$; $a = 5.8697(9)$, $b = 47.357(7)$, $c = 6.3587(10)$ Å, $\beta = 109.492(3)°$, $U = 1666.2(4)$ Å^3, $T = 200(2)$ K, $Z = 2$, μ(Mo-Kα) = 0.093 mm^{-1}, $D_c = 1.337$ Mg/m^3, $\lambda = 0.71073$ Å, $F(000) = 704$, $2\theta_{max} = 21.69°$, 6977 reflections measured, 2383 unique ($R_{int} = 0.0383$). Final residuals for 238 parameters were $R_1 = 0.0686$, $wR_2 = 0.1395$ for $I>2\sigma(I)$, and $R_1 = 0.1403$, $wR_2 = 0.1709$ for all 2383 data.

Crystal packing: The co-crystal contains flurbiprofen:1,2-bis (4-pyridyl) ethylene heterodimers, sustained by two hydrogen bonded carboxylic acid-pyridine supramolecular synthons, arranged in a herringbone motif that packs in the space group $P2_1/n$. The heterodimer from 1,2-bis (4-pyridyl) ethylene further extends the homodimer relative to example 21 and packs to form a two-dimensional network sustained by π-π stacking and hydrophobic interactions of the bipyridine and phenyl groups of the flurbiprofen.

Infrared Spectroscopy: (Nicolet Avatar 320 FTIR), aromatic C-H stretching at 2927 cm^{-1} and 2850 cm^{-1}; N--H bending and scissoring at 1875 cm^{-1}; C=O stretching at 1707 cm^{-1}; C=C and C=N ring stretching at 1483 cm^{-1}.

Differential Scanning Calorimetry: (TA Instruments 2920 DSC), 100.01 degrees C, 125.59 degrees C and 163.54 degrees C (endotherms); m.p. = 153-158 degrees C (MEL-TEMP); (flurbiprofen m.p. = 110-111 degrees C, trans-1, 2-bis (4-pyridyl) ethylene m.p. = 150-153 degrees C).

Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA), 91.79% weight loss starting at 133.18 degrees C followed by complete decomposition.

Powder x-ray diffraction: (Rigaku Miniflex Diffractometer using Cu Kα ($\lambda = 1.540562$), 30kV, 15mA), the powder data were collected over an angular range of 3° to 40° 2θ in continuous scan mode using a step size of 0.02° 2θ and a scan speed of 2.0°/minute. PXRD derived from the single crystal data, experimental (calculated): 3.6 (3.7); 17.3 (17.7); 18.1 (18.6); 18.4 (18.6); 19.1 (19.3); 22.3 (22.5); 23.8 (23.9); 25.9 (26.4); 28.1 (28.5).

Example 23

Carbamazepine:*p*-Phthalaldehyde (2:1 stoichiometry)

25 mg (0.1058 mmol) carbamazepine and 7 mg (0.0521 mmol) *p*-phthalaldehyde were dissolved in approximately 3 mL methanol. Slow evaporation of the solvent yielded colorless needles of a 2:1 carbamazepine:*p*-phthalaldehyde co-crystal, as shown in Figs. 44A-B.

Crystal data: (Bruker SMART-APEX CCD Diffractometer), $C_{38}H_{30}N_4O_4$, M = 606.66, monoclinic *C2/c*; a = 29.191(16), b = 4.962(3), c = 20.316(11) Å, β = 92.105(8)°, U = 2941(3) Å^3, T= 200(2) K, Z = 4, μ(Mo-Kα) = 0.090 mm^{-1}, D_c = 1.370 Mg/m^3, λ = 0.71073 Å, F(000) = 1272, $2\theta_{max}$ = 43.66°, 3831 reflections measured, 1559 unique (R_{int} = 0.0510). Final residuals for 268 parameters were R_1 = 0.0332, wR_2 = 0.0801 for I>2σ(I), and R_1 = 0.0403, wR_2 = 0.0831 for all 1559 data.

Crystal packing: The co-crystals contain hydrogen bonded carboxamide homodimers that crystallize in the space group *C2/c*. The 1° amines of the homodimer are bifurcated to the carbonyl of the *p*-phthalaldehyde forming a chain with an adjacent homodimer. The chains pack in a crinkled tape motif sustained by π-π interactions between phenyl rings of the carbamazepine.

Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). The 1° amine unsymmetrical and symmetrical stretching was shifted down to 3418 cm^{-1}; aliphatic aldehyde and 1° amide C=O stretching was shifted up to 1690 cm^{-1}; N-H in-plane bending at 1669 cm^{-1}; C-H aldehyde stretching at 2861 cm^{-1} and H-C=O bending at 1391 cm^{-1}.

Differential Scanning Calorimetry: (TA Instruments 2920 DSC), 128.46 degrees C (endotherm), m.p. = 121-124 degrees C (MEL-TEMP), (carbamazepine m.p. = 190.2 degrees C, *p*-phthalaldehyde m.p. = 116 degrees C).

Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA), 17.66% weight loss starting at 30.33 degrees C then a 17.57% weight loss starting at 100.14 degrees C followed by complete decomposition.

Powder x-ray diffraction: (Rigaku Miniflex Diffractometer using Cu Kα (λ = 1.540562), 30kV, 15mA). The powder data were collected over an angular range of 3° to 40° 2θ in continuous scan mode using a step size of 0.02° 2θ and a scan speed of

2.0°/minute. PXRD derived from the single crystal data, experimental (calculated): 8.5 (8.7); 10.6 (10.8); 11.9 (12.1); 14.4 (14.7) 15.1 (15.2); 18.0 (18.1); 18.5 (18.2); 19.8 (18.7); 23.7 (24.0); 24.2 (24.2); 26.4 (26.7); 27.6 (27.9); 27.8 (28.2); 28.7 (29.1); 29.3 (29.6); 29.4 (29.8).

Example 24

Carbamazepine:nicotinamide (1:1 stoichiometry)

25 mg (0.1058 mmol) carbamazepine and 12 mg (0.0982 mmol) nicotinamide were dissolved in 4 mL of DMSO, methanol or ethanol. Slow evaporation of the solvent yielded colorless needles of a 1:1 carbamazepine:nicotinamide co-crystal, as shown in Fig. 45.

Using a separate method, 25 mg (0.1058 mmol) carbamazepine and 12 mg (0.0982mmol) nicotinamide were ground together with mortar and pestle. The solid was determined to be 1:1 carbamazepine:nicotinamide microcrystals (PXRD).

1:1 carbamazepine:nicotinamide co-crystals were also prepared via another method. A 12-block experiment was designed with 12 solvents. (A block is a receiving plate, which can be an industry standard 96 well, 384 well, or 1536 well format, or a custom format.) 1152 crystallization experiments were carried out using the CrystalMax™ platform. The co-crystal was obtained from samples containing toluene, acetone, or isopropyl acetate. The resulting co-crystal was characterized by PXRD and DSC and these data are shown in Figs. 46 and 47, respectively. The co-crystals prepared from toluene, aceone, or isopropyl acetate may contain impurities such as carbamazepine in free form due to incomplete purification.

Crystal data: (Bruker SMART-APEX CCD Diffractometer), $C_{21}H_{18}N_4O_2$, $M = 358.39$, monoclinic $P2_1/n$; $a = 5.0961(8)$, $b = 17.595(3)$, $c = 19.647(3)$ Å, $\beta = 90.917(3)°$, $U = 1761.5(5)$ Å^3, $T = 200(2)$ K, $Z = 4$, μ(Mo-Kα) = 0.090 mm^{-1}, $D_c = 1.351$ Mg/m^3, $\lambda = 0.71073$ Å, $F(000) = 752$, $2\theta_{max} = 56.60°$, 10919 reflections measured, 4041 unique ($R_{int} = 0.0514$). Final residuals for 248 parameters were $R_1 = 0.0732$, $wR_2 = 0.1268$ for $I>2\sigma(I)$, and $R_1 = 0.1161$, $wR_2 = 0.1430$ for all 4041 data.

Crystal packing: The co-crystals contain hydrogen bonded carboxamide homodimers. The 1° amines are bifurcated to the carbonyl of the nicotinamide on each side of the dimer. The 1° amines of each nicotinamide are hydrogen bonded to the carbonyl of the adjoining dimer. The dimers form chains with π-π interactions from the phenyl groups of the carbamazepine.

Infrared Spectroscopy: (Nicolet Avatar 320 FTIR), unsymmetrical and symmetrical stretching shifts down to 3443 cm^{-1} and 3388 cm^{-1} accounting for 1° amines; 1° amide C=O stretching at 1690 cm^{-1}; N-H in-plane bending at 1614 cm^{-1}; C=C stretching shifted down to 1579 cm^{-1}; aromatic H's from 800 cm^{-1} to 500 cm^{-1} are present.

Differential Scanning Calorimetry: (TA Instruments 2920 DSC), 74.49 degrees C (endotherm) and 159.05 degrees C (endotherm), m.p. = 153-158 degrees C (MEL-TEMP), (carbamazepine m.p. = 190.2 degrees C, nicotinamide m.p. = 150-160 degrees C).

Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA), 57.94% weight loss starting at 205.43 degrees C followed by complete decomposition.

Powder x-ray diffraction: (Rigaku Miniflex Diffractometer using Cu Kα (λ = 1.540562), 30kV, 15mA). The powder data were collected over an angular range of 3° to 40° 2θ in continuous scan mode using a step size of 0.02° 2θ and a scan speed of 2.0°/minute. PXRD: Showed analogous peaks to the simulated PXRD derived from the single crystal data. PXRD analysis experimental (calculated): 6.5 (6.7); 8.8 (9.0); 10.1 (10.3); 13.2 (13.5); 15.6 (15.8); 17.7 (17.9); 17.8 (18.1); 18.3 (18.6); 19.8 (20.1); 20.4 (20.7); 21.6 (N/A); 22.6 (22.8); 22.9 (23.2); 26.4 (26.7); 26.7 (27.0); 28.0 (28.4).

Example 25

Carbamazepine:saccharin (1:1 stoichiometry)

25 mg (0.1058mmol) carbamazepine and 19 mg (0.1037 mmol) saccharin were dissolved in approximately 4 mL ethanol. Slow evaporation of the solvent yielded colorless needles of a 1:1 carbamazepine:saccharin co-crystal, as shown in Fig. 48. Solubility measurements indicate that this co-crystal of carbamazepine has improved

solubility over previously known forms of carbamazepine (*e.g.*, increased molar solubility and longer solubility in aqueous solutions).

1:1 carbamazepine:saccharin co-crystals were also prepared via another method. A 12-block experiment was designed with 12 solvents. (A block is a receiving plate, which can be an industry standard 96 well, 384 well, or 1536 well format, or a custom format.) 1152 crystallization experiments were carried out using the CrystalMax™ platform. The carbamazepine:saccharin co-crystal was obtained from a mixture of isopropyl acetate and heptane. The resulting co-crystal was characterized by PXRD and DSC and these data are shown in Figures 49 and 50, respectively. The co-crystal prepared from a mixture of isopropyl acetate and heptane may contain impurities such as carbamazepine in free form due to incomplete purification.

Crystal data: (Bruker SMART-APEX CCD Diffractometer), $C_{22}H_{17}N_3O_4S$, M = 419.45, triclinic *P-1*; a = 7.5140(11), b = 10.4538(15), c = 12.6826(18) Å, $\alpha = 83.642(2)°$, $\beta = 85.697(2)°$, $\gamma = 75.411(2)°$, $U = 957.0(2)$ Å^3, T = 200(2) K, Z = 2, μ(Mo-Kα) = 0.206 mm^{-1}, $D_c = 1.456$ Mg/m^3, $\lambda = 0.71073$ Å, F(000) = 436, $2\theta_{max} = 56.20°$; 8426 reflections measured, 4372 unique ($R_{int} = 0.0305$). Final residuals for 283 parameters were $R_1 = 0.0458$, $wR_2 = 0.1142$ for $I>2\sigma(I)$, and $R_1 = 0.0562$, $wR_2 = 0.1204$ for all 4372 data.

Crystal packing: The co-crystals contain hydrogen bonded carboxamide homodimers. The 2° amines of the saccharin are hydrogen bonded to the carbonyl of the carbamazepine on each side forming a tetramer. The crystal has a space group of *P-1* with π-π interactions between the phenyl groups of the carbamazepine and the saccharin phenyl groups.

Infrared Spectroscopy: (Nicolet Avatar 320 FTIR), unsymmetrical and symmetrical stretching shifts up to 3495 cm^{-1} accounting for 1° amines; C=O aliphatic stretching was shifted up to 1726 cm^{-1}; N-H in-plane bending at 1649 cm^{-1}; C=C stretching shifted down to 1561 cm^{-1}; (O=S=O) sulfonyl peak at 1330 cm^{-1} C-N aliphatic stretching 1175 cm^{-1}.

Differential Scanning Calorimetry: (TA Instruments 2920 DSC), 75.31 degrees C (endotherm) and 177.32 degrees C (endotherm), m.p. = 148-155 degrees C (MEL-TEMP); (carbamazepine m.p. = 190.2 degrees C, saccharin m.p. = 228.8 degrees C).

Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA), 3.342% weight loss starting at 67.03 degrees C and a 55.09% weight loss starting at 118.71 degrees C followed by complete decomposition.

Powder x-ray diffraction: (Rigaku Miniflex Diffractometer using Cu Kα (λ = 1.540562), 30kV, 15mA). The powder data were collected over an angular range of 3° to 40° 2θ in continuous scan mode using a step size of 0.02° 2θ and a scan speed of 2.0 °/minute. PXRD derived from the single crystal data, experimental (calculated): 6.9 (7.0); 12.2 (12.2); 13.6 (13.8); 14.0 (14.1); 14.1 (14.4); 15.3 (15.6); 15.9 (15.9); 18.1 (18.2); 18.7 (18.8); 20.2 (20.3); 21.3 (21.5); 23.7 (23.9); 26.3 (26.4); 28.3 (28.3).

Example 26

Carbamazepine:2,6-pyridinedicarboxylic acid (1:1 stoichiometry)

36 mg (0.1524 mmol) carbamazepine and 26 mg (0.1556 mmol) 2,6-pyridinedicarboxylic acid were dissolved in approximately 2 mL ethanol. Slow evaporation of the solvent yielded clear needles of a 1:1 carbamazepine:2,6-pyridinedicarboxylic acid co-crystal, as shown in Figs. 51A-B.

Crystal data: (Bruker SMART-APEX CCD Diffractometer). $C_{22}H_{17}N_3O_5$, M=403.39, orthorhombic P2(1)2(1)2(1); a=7.2122, b=14.6491, c=17.5864 Å, α=90°, β=90°, γ=90°, U=1858.0(2) Å^3, T=100 K, Z=4, μ(MO-Kα)=0.104 mm^{-1}, D_c=1.442 Mg/m^3, λ=0.71073Å, F(000)840, $2\theta_{max}$=28.3. 16641 reflections measured, 4466 unique (R_{int}=0.093). Final residuals for 271 parameters were R_1=0.0425 and wR_2=0.0944 for I>2σ(I).

Crystal packing: Each hydrogen on the carbamazepine 1° amine is hydrogen bonded to a carbonyl group of a different 2,6-pyridinedicarboxylic acid moiety. The carbonyl of the carbamazepine carboxamide is hydrogen bonded to two hydroxide groups of one 2,6-pyridinedicarboxylic acid moiety.

Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). 3439 cm^{-1}, (N-H stretch, 1° amine, carbamazepine); 1734 cm^{-1}, (C=O); 1649 cm^{-1}, (C=C).

Melting Point: 214-216 degrees C (MEL-TEMP). (carbamazepine m.p. = 191-192 degrees C, 2,6-pyridinedicarboxylic acid m.p. = 248-250 degrees C).

Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA). 69% weight loss starting at 215 degrees C and a 17% weight loss starting at 392 degrees C followed by complete decomposition.

Example 27

Carbamazepine:5-nitroisophthalic acid (1:1 stoichiometry)

40 mg (0.1693 mmol) carbamazepine and 30 mg (0.1421 mmol) 5-nitroisophthalic acid were dissolved in approximately 3 mL methanol or ethanol. Slow evaporation of the solvent yielded yellow needles of a 1:1 carbamazepine:5-nitroisophthalic acid co-crystal, as shown in Figs. 52A-B.

Crystal data: (Bruker SMART-APEX CCD Diffractometer). monoclinic C2/c; a=34.355(8), b=5.3795(13), c=23.654(6) Å, α=90°, β=93.952(6)°, γ=90°, U=4361.2(18)Å^3, T=200(2) K, Z=4, μ(MO-Kα)=0.110 mm^{-1}, D_c=1.439 Mg/m^3, λ=0.71073Å , F(000)1968, $2\theta_{max}$=26.43°. 11581 reflections measured, 4459 unique (R_{int}=0.0611). Final residuals for 311 parameters were R_1=0.0725, wR_2=0.1801 for I>2σ(I), and R_1=0.1441, wR_2=0.1204 for all 4459 data.

Crystal packing: The co-crystals are sustained by hydrogen bonded carboxylic acid homodimers between the two 5-nitroisophthalic acid moieties and hydrogen bonded carboxy-amide heterodimers between the carbamazepine and 5-nitroisophthalic acid moiety. There is solvent hydrogen bonded to an additional N-H donor from the carbamazepine moiety.

Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). 3470 cm^{-1}, (N-H stretch, 1° amine, carbamazepine); 3178 cm^{-1}, (C-H stretch, alkene); 1688 cm^{-1}, (C=O); 1602 cm^{-1}, (C=C).

Differential Scanning Calorimetry: (TA Instruments 2920 DSC). 190.51 degrees C (endotherm). m.p. = NA (decomposes at 197-200 degrees C) (MEL-TEMP). (carbamazepine m.p. = 191-192 degrees C, 5-nitroisophthalic acid m.p. = 260-261 degrees C).

Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA). 32.02% weight loss starting at 202 degrees C, a 12.12% weight loss starting at 224

degrees C and a 17.94% weight loss starting at 285 degrees C followed by complete decomposition.

Powder x-ray diffraction: (Rigaku Miniflex Diffractometer using CuKα (λ=1.540562), 30kV, 15mA). The powder data were collected over an angular range of 3 to 40 2 in continuous scan mode using a step size of 0.02 2 and a scan speed of 2.0 /min. PXRD: Showed analogous peaks to the simulated PXRD derived from the single crystal data. PXRD analysis experimental (calculated): 10.138 (10.283), 15.291 (15.607), 17.438 (17.791), 21.166 (21.685), 31.407 (31.738), 32.650 (32.729).

Example 28

Carbamazepine:1,3,5,7-adamantane tetracarboxylic acid (2:1 stoichiometry)

15 mg (0.1524 mmol) carbamazepine and 20 mg (0.1556 mmol) 1,3,5,7-adamantanetetracarboxylic acid were dissolved in approximately 1 mL methanol or 1 mL ethanol. Slow evaporation of the solvent yields clear plates of a 2:1 carbamazepine:1,3,5,7-adamantanetetracarboxylic acid co-crystal, as shown in Figs. 53A-B.

Crystal data: (Bruker SMART-APEX CCD Diffractometer). $C_{44}H_{40}N_4O_{10}$, M=784.80, monoclinicC2/c; a=18.388(4), b=12.682(3), c=16.429(3) Å, β=100.491(6)°, U=3767.1(14) $Å^3$, T=100(2) K, Z=4, μ(MO-Kα)=0.099 mm^{-1}, D_c=1.384 Mg/m^3, λ=0.71073Å , F(000)1648, $2\theta_{max}$=28.20°. 16499 reflections measured, 4481 unique (R_{int}=0.052). Final residuals for 263 parameters were R_1=0.0433 and wR_2=0.0913 for I>2σ(I).

Crystal packing: The co-crystals form a single 3D network of four tetrahedron, linked by square planes similar to the *PtS* topology. The crystals are sustained by hydrogen bonding.

Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). 3431 cm^{-1}, (N-H stretch, 1° amine, carbamazepine); 3123 cm^{-1}, (C-H stretch, alkene); 1723 cm^{-1}, (C=O); 1649 cm^{-1}, (C=C).

Melting Point: (MEL-TEMP). 258-260 degrees C (carbamazepine m.p. = 191-192 degrees C, adamantanetetracarboxylic acid m.p. = >390 degrees C).

Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA). 9% weight loss starting at 189 degrees C, a 52% weight loss starting at 251 degrees C and a 31% weight loss starting at 374 degrees C followed by complete decomposition.

Example 29

Carbamazepine:benzoquinone (1:1 stoichiometry)

25 mg (0.1058 mmol) carbamazepine and 11 mg (0.1018 mmol) benzoquinone was dissolved in 2 mL methanol or THF. Slow evaporation of the solvent produced an average yield of yellow crystals of a 1:1 carbamazepine:benzoquinone co-crystal, as shown in Figs. 54A-B.

Crystal data: (Bruker SMART-APEX CCD Diffractometer). $C_{21}H_{16}N_2O_3$, M=344.36, monoclinic P2(1)/c; a=10.3335(18), b=27.611(5), c=4.9960(9) Å, β=102.275(3)°, U=1392.9(4) Å^3, T=100(2) K, Z=3, D_c=1.232 Mg/m^3, μ(MO-Kα)=0.084 mm^{-1}, λ=0.71073Å , F(000)540, $2\theta_{max}$=28.24°. 8392 reflections measured, 3223 unique (R_{int}=0.1136). Final residuals for 199 parameters were R_1=0.0545 and wR_2=0.1358 for I>2σ(I), and R_1=0.0659 and wR_2=0.1427 for all 3223 data.

Crystal packing: The co-crystals contain hydrogen bonded carboxamide homodimers. Each 1° amine on the carbamazepine is bifurcated to a carbonyl group of a benzoquinone moiety. The dimers form infinite chains.

Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). 3420 cm^{-1}, (N-H stretch, 1° amine, carbamazepine); 2750 cm^{-1}, (aldehyde stretch); 1672 cm^{-1}, (C=O); 1637 cm^{-1}, (C=C, carbamazepine).

Melting Point: 170 degrees C (MEL-TEMP). (carbamazepine m.p. = 191-192 degrees C, benzoquinone m.p. = 115.7 degrees C).

Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA). 20.62% weight loss starting at 168 degrees C and a 78% weight loss starting at 223 degrees C followed by complete decomposition.

Example 30

Carbamazepine:trimesic acid (1:1 stoichiometry)

36 mg (0.1524 mmol) carbamazepine and 31 mg (0.1475 mmol) trimesic acid were dissolved in a solvent mixture of approximately 2 mL methanol and 2 mL dichloromethane. Slow evaporation of the solvent mixture yielded white starbursts of a 1:1 carbamazepine:trimesic acid co-crystal, as shown in Figs. 55A-B.

1:1 carbamazepine:trimesic acid co-crystals were also prepared via another method. A 9-block experiment was designed with 10 solvents. 864 crystallization experiments with 8 co-crystal formers and 3 concentrations were carried out using the CrystalMax™ platform. The co-crystal was obtained from samples containing methanol. The resulting co-crystal was characterized by PXRD and the diffractogram is shown in Fig. 56.

Crystal data: (Bruker SMART-APEX CCD Diffractometer). $C_{24}H_{18}N_2O_7$, M=446.26, monoclinic C2/c; a=32.5312(50), b=5.2697(8), c=24.1594(37) Å,α=90°, β=98.191(3)°, γ=90°, U=4099.39(37) Å^3, T=-173 K, Z=8, μ(MO-Kα)=0.110 mm^{-1}, D_c=1.439 Mg/m^3, λ=0.71073Å, F(000)1968, $2\theta_{max}$=26.43°. 11581 reflections measured, 4459 unique (R_{int}=0.0611). Final residuals for 2777 parameters were R_1=0.1563, wR_2=0.1887 for I>2σ(I), and R_1=0.1441, wR_2=0.1204 for all 3601 data.

Crystal packing: The co-crystals are sustained by hydrogen bonded carboxylic acid homodimers between carbamazepine and trimesic acid moieties and hydrogen bonded carboxylic acid-amine heterodimers between two trimesic acid moieties arranged in a stacked ladder formation.

Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). 3486 cm^{-1}(N-H stretch, 1° amine, carbamazepine); 1688 cm^{-1} (C=O, 1° amide stretch, carbamazepine); 1602 cm^{-1} (C=C, carbamazepine).

Differential Scanning Calorimetry: (TA Instruments 2920 DSC). 273 degrees C (endotherm). m.p. = NA, decomposes at 278 degrees C (MEL-TEMP). (carbamazepine m.p. = 191-192 degrees C, trimesic acid m.p. = 380 degrees C)

Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA). 62.83% weight loss starting at 253 degrees C and a 30.20% weight loss starting at 278 degrees C followed by complete decomposition.

Powder x-ray diffraction: (Rigaku Miniflex Diffractometer using CuKα (λ=1.540562), 30kV, 15mA). The powder data were collected over an angular range of 3 to 40 degrees 2-theta in continuous scan mode using a step size of 0.02 degrees 2-theta and a scan speed of 2.0/min. PXRD analysis experimental: 10.736, 12.087, 16.857, 24.857, 27.857.

Table XXIV. Detailed Characterization of Co-Crystals
All PXRD peaks are in units of degrees 2-theta All Raman shifts are in units of cm^{-1}
Celecoxib:Nicotinamide (Example 1) PXRD: 3.77, 7.56, 9.63, 14.76, 15.21, 16.01, 17.78, 18.68, 19.31, 20.44, 21.19, 22.10 DSC: Two endothermic transitions at about 117 and 119 degrees C and a sharp endotherm at about 130 degrees C TGA: Decomposition beginning at about 150 degrees C Raman: 1618, 1599, 1452, 1370, 1163, 1044, 973, 796, 632, 393, 206
Celecoxib:18-Crown-6 (Example 2) PXRD: 8.73, 11.89, 12.57, 13.13, 15.01, 16.37, 17.03, 17.75, 18.45, 20.75, 22.37, 23.11, 24.33, 24.97, 26.61, 28.15 DSC: Sharp endotherm at about 190 degrees C TGA: Decomposition above 200 degrees C with a 25% weight loss between about 190-210 degrees C
Topiramate:18-Crown-6 (Example 3) PXRD: 10.79, 11.07, 12.17, 13.83, 16.13, 18.03, 18.51, 18.79, 19.21, 21.43, 22.25, 24.11 DSC: Sharp endotherm at about 135 degrees C TGA: Rapid decomposition beginning at about 135 degrees C and leveling off slightly after 200 degrees C Raman: 2995, 2943, 1472, 1427, 1262, 849, 805, 745, 629, 280, 226
Olanzapine:Nicotinamide (Example 4) PXRD (Form I): 4.89, 8.65, 12.51, 14.19, 15.59, 17.15, 19.71, 21.05, 23.95, 24.59, 25.53, 26.71 PXRD (Form II): 5.13, 8.65, 11.87, 14.53, 17.53, 18.09, 19.69, 24.19, 26.01 (data as received) PXRD (Form III): 6.41, 12.85, 14.91, 18.67, 21.85, 24.37 DSC (Form I): Slightly broad endotherm at about 126 degrees C
cis-Itraconazole:Succinic Acid (Example 5) PXRD: 3.01, 6.01, 8.13, 9.05, 15.87, 16.17, 17.29, 24.47 DSC: Single endothermic transition at about 160 degrees C ± 1.0 degrees C TGA: Less than 0.1 % volatile components by weight

cis-Itraconazole:Fumaric Acid (Example 6) PXRD: 4.61, 5.89, 9.23, 10.57, 15.51, 16.23, 16.93, 19.05, 20.79 DSC: The material had a weak endothermic transition at about 142 degrees C and a strong endothermic transition at about 180 degrees C TGA: The sample loses 0.5 % of its weight on the TGA between room temperature and 100 degrees C
cis-Itraconazole:L-Tartaric Acid (Example 7) PXRD: 4.13, 6.19, 8.49, 16.13, 17.23, 18.07, 19.13, 20.79, 22.85, 26.17 DSC: An endothermic transition at about 181 degrees C TGA: Less than 0.1 % volatile components by weight by TGA
cis-Itraconazole:L-Malic acid (Example 8) PXRD: 4.43, 6.07, 8.85, 15.93, 17.05, 20.49, 21.27, 22.85, 23.17, 26.17 DSC: The sample has a strong endothermic transition at about 154 degrees C TGA: The sample contained less than 0.1% volatile components by weight
cis-ItraconazoleHCl:DL-Tartaric acid (Example 9) PXRD: 3.73, 10.95, 13.83, 16.53, 17.75, 19.65, 21.11, 23.95 DSC: The sample has a peak endothermic transition at about 162 degrees C TGA: The sample contained less than 0.1 % volatile components by weight
Modafinil:Malonic acid (Example 10) PXRD (Form I): 5.11, 9.35, 16.87, 18.33, 19.53, 21.38, 22.05, 22.89, 24.73, 25.19, 25.81, 28.59 PXRD (Form II): 5.90, 9.54, 15.79, 18.02, 20.01, 21.66, 22.47, 25.30 DSC (Form I): Endothermic transition at about 106 degrees C Raman (Form I): 1601, 1183, 1032, 1004, 814, 633, 265, 222
Modafinil:Glycolic acid (Example 11) PXRD: 6.09, 9.51, 14.91, 15.97, 19.01, 20.03, 21.59, 22.43, 22.75, 23.75, 25.03, 25.71
Modafinil:Maleic acid (Example 12) PXRD: 4.69, 6.15, 9.61, 10.23, 15.65, 16.53, 17.19, 18.01, 19.27, 19.53, 19.97, 21.83, 22.45, 25.65
5-fluorouracil:Urea (Example 13) PXRD: 11.23, 12.69, 13.27, 15.93, 16.93, 20.37, 23.65, 25.55, 26.87, 32.49 DSC: Sharp endotherm at about 208 degrees C TGA: Approximately 32 percent weight loss between 150 and 220 degrees C Raman: 1347, 1024, 757, 644, 545
Hydrochlorothiazide:Nicotinic acid (Example 14) PXRD: 8.57, 13.23, 14.31, 16.27, 17.89, 18.75, 21.13, 21.45, 24.41, 25.73, 26.57, 27.43
Hydrochlorothiazide:18-crown-6 (Example 15) PXRD: 9.97, 10.43, 11.57, 11.81, 12.83, 14.53, 15.67, 16.61, 19.05, 20.31, 20.65, 21.09, 21.85, 22.45, 23.63, 24.21, 25.33, 26.73
Hydrochlorothiazide:Piperazine (Example 16) PXRD: 6.85, 13.75, 15.93, 18.71, 20.67, 20.93, 23.27, 24.17, 28.33, 28.87, 30.89
Acetaminophen:4,4'-Bipyridine:water (Example 17) DSC: Endothermic transition at about 58 degrees C

Phenytoin:Pyridone (Example 18) PXRD: 5.2, 11.1, 15.1, 16.2, 16.7, 17.8, 19.4, 19.8, 20.3, 21.2, 23.3, 26.1, 26.4, 27.3, 29.5 DSC: Endothermic transitions at about 233 and 271 degrees C TGA: 29.09 percent weight loss starting at about 193 degrees C, 48.72 percent weight loss starting at about 238 degrees C, 18.38 percent weight loss starting at about 260 degrees C
Aspirin:4,4'-Bipyridine (Example 19) DSC: Endothermic transition at about 95 degrees C TGA: 9 percent weight loss starting at about 23 degrees C, 49.06 percent weight loss starting at about 103 degrees C, decomposition starting at about 209 degrees C
Ibuprofen:4,4'-Bipyridine (Example 20) PXRD: 3.4, 6.9, 10.4, 17.3, 19.1 DSC: Endothermic transitions at about 65 and 119 degrees C TGA: 13.28 percent weight loss between room temperature and about 100 degrees C
Flurbiprofen:4,4'-Bipyridine (Example 21) PXRD: 16.8, 17.1, 18.1, 19.0, 20.0, 21.3, 22.7, 25.0, 26.0, 26.1, 28.2, 29.1 DSC: Endothermic transition at about 162 degrees C TGA: 30.93 percent weight loss starting at about 31 degrees C, 46.26 percent weight loss starting at about 169 degrees C
Flurbiprofen:trans-1,2-bis (4-pyridyl) ethylene (Example 22) PXRD: 3.6, 17.3, 18.1, 18.4, 19.1, 22.3, 23.8, 25.9, 28.1 DSC: Endothermic transitions at about 100, 126, and 164 degrees C TGA: 91.79 percent weight loss starting at about 133 degrees C
Carbamazepine:p-phthalaldehyde (Example 23) PXRD: 8.5, 10.6, 11.9, 14.4, 15.1, 18.0, 18.5, 19.8, 23.7, 24.2, 26.4, 27.6, 27.8, 28.7, 29.3, 29.4 DSC: Endothermic transition at about 128 degrees C TGA: 17.66 percent weight loss starting at about 30 degrees C, 17.57 percent weight loss starting at about 100 degrees C
Carbamazepine:Nicotinamide (Example 24) PXRD: 6.5, 8.8, 10.1, 13.2, 15.6, 17.7, 17.8, 18.3, 19.8, 20.4, 21.6, 22.6, 22.9, 26.4, 26.7, 28.0 DSC: Sharp endotherm at about 157 degrees C TGA: Decomposition beginning at about 150 degrees C
Carbamazepine:Saccharin (Example 25) PXRD: 6.9, 12.2, 13.6, 14.0, 14.1, 15.3, 15.9, 18.1, 18.7, 20.2, 21.3, 23.7, 26.3, 28.3 DSC: Endotherms were present at about 75 and 177 degrees C TGA: 3.342 percent weight loss starting at about 67 degrees C, 55.09 percent weight loss starting at about 119 degrees C
Carbamazepine:2,6-pyridinecarboxylic acid (Example 26) TGA: 69 percent weight loss starting at about 215 degrees C, 17 percent weight loss starting at about 392 degrees C

Carbamazepine:5-nitroisophthalic acid (Example 27) PXRD: 10.14, 15.29, 17.44, 21.17, 31.41, 32.65 DSC: Endotherm at about 191 degrees C TGA: 32.02 percent weight loss starting at about 202 degrees C, 12.12 percent weight loss starting at about 224 degrees C, 17.94 percent weight loss starting at about 285 degrees C
Carbamazepine:1,3,5,7-adamantane tetracarboxylic acid (Example 28) TGA: 9 percent weight loss starting at about 189 degrees C, 52 percent weight loss starting at about 251 degrees C, 31 percent weight loss starting at about 374 degrees C
Carbamazepine:Benzoquinone (Example 29) TGA: 20.62 percent weight loss starting at about 168 degrees C, 78 percent weight loss starting at about 223 degrees C
Carbamazepine:Trimesic acid (Example 30) PXRD: 10.89, 12.23, 14.83, 16.25, 17.05, 18.13, 18.47, 21.47, 21.95, 24.57, 25.11, 27.99 DSC: Endothermic transition at about 273 degrees C TGA: 62.83 percent weight loss starting at about 253 degrees C, 30.20 percent weight loss starting at about 278 degrees C

Example 31

A co-crystal with a modulated dissolution profile has been prepared. Celecoxib: nicotinamide co-crystals were prepared via methods shown in Example 1. (See Fig. 57)

Example 32

A co-crystal with a modulated dissolution profile has been prepared. *cis*-Itraconazole: succinic acid, *cis*-itraconazole:L-tartaric acid and *cis*-itraconazole:L-malic acid co-crystals were prepared via methods shown in Examples 5, 7 and 8. (See Fig. 58)

Example 33

A co-crystal of an unsaltable or difficult to salt API has been prepared. Celecoxib: nicotinamide co-crystals were prepared via methods shown in Example 1.

Example 34

A co-crystal with an improved hygroscopicity profile has been prepared. Celecoxib: nicotinamide co-crystals were prepared via methods shown in Example 1. (See Fig. 59)

Example 35

A co-crystal with reduced form diversity as compared to the API has been prepared. Co-crystals of carbamazepine and saccharin have been prepared via method shown in Example 25.

Example 36

The formulation of a modafinil:malonic acid form I co-crystal was completed using lactose. Two mixtures, one of modafinil and lactose, and the second of modafinil:malonic acid co-crystal and lactose, were ground together in a mortar an pestle. The mixtures targeted a 1:1 weight ratio of modafinil to lactose. In the modafinil and lactose mixture, 901.2 mg of modafinil and 901.6 mg of lactose were ground together. In the modafinil:malonic acid co-crystal and lactose mixture, 1221.6 mg of co-crystal and 871.4 mg of lactose were ground together. The resulting powders were analyzed by PXRD and DSC. The PXRD patterns and DSC thermograms of the mixtures showed virtually no change upon comparison with both individual components. The DSC of the co-crystal mixture showed only the co-crystal melting peak at 113.6 degrees C with a heat of fusion of 75.9 J/g. This heat of fusion is 59.5 % of that found for the co-crystal alone (127.5 J/g). This result is consistent with a 58.4 % weight ratio of co-crystal in the mixture. The DSC of the modafinil and lactose mixture had a melting point of 165.7 degrees C. This is slightly lower then the measured melting point of modafinil (168.7 degrees C). The heat of fusion of the mixture (59.3 J/g) is 46.9 % that of the modafinil alone (126.6 J/g), which is consistent with the estimated value of 50 %.

The *in vitro* dissolution of both the modafinil:malonic acid form I co-crystal and pure modafinil were tested in capsules. Both gelatin and hydroxypropylmethyl cellulose

(HPMC) capsules were used in the dissolution study. The capsules were formulated with and without lactose. All formulations were ground in a mortar and pestle prior to transfer into a capsule. The dissolution of the capsules was tested in 0.01 M HCl (See Figure 61).

In 0.01M HCl, using sieved and ground materials in gelatin capsules:

Modafinil and the modafinil:malonic acid form I co-crystal were passed through a 38 micrometer sieve. Gelatin capsules (Size 0, B&B Pharmaceuticals, Lot # 15-01202) were filled with 200.0 mg sieved modafinil, 280.4 mg sieved modafinil:malonic acid co-crystal, 200.2 mg ground modafinil, or 280.3 mg ground modafinil:malonic acid co-crystal. Dissolution studies were performed in a Vankel VK 7000 Benchsaver Dissolution Testing Apparatus with the VK750D heater/circulator set at 37 degrees C. At 0 minutes, the capsules were dropped into vessels containing 900 mL 0.01 M HCl and stirred by paddles.

Absorbance readings were taken using a Cary 50 Spectrophotometer (wavelength set at 260nm) at the following time points: 0, 5, 10, 15, 20, 25, 30, 40, 50, and 60 minutes. The absorbance values were compared to those of standards and the modafinil concentrations of the solutions were calculated.

In 0.01M HCl, using ground materials in gelatin or HPMC capsules, with and without lactose:

Modafinil and the modafinil:malonic acid form I co-crystal were mixed with equivalent amounts of lactose (Spectrum, Lot QV0460) for approximately 5 minutes. Gelatin capsules (Size 0, B&B Pharmaceuticals, Lot # 15-01202) were filled with 400.2 mg modafinil and lactose (approximately 200 mg modafinil), or 561.0 mg modafinil:malonic acid form I co-crystal and lactose (approximately 200 mg modafinil). HPMC capsules (Size 0, Shionogi, Lot # A312A6) were filled with 399.9 mg modafinil and lactose, 560.9 mg modafinil:malonic acid co-crystal and lactose, 199.9 mg modafinil, or 280.5 mg modafinil:malonic acid form I co-crystal. The dissolution study was carried out as described above.

Example 37

The modafinil:malonic acid form I co-crystal (from Example 10) was administered to dogs in a pharmacokinetic study. Particles of modafinil:malonic acid co-crystal with a median particle size of about 16 micrometers were administered in the study. As a reference, micronized modafinil with a median particle size of about 2 micrometers was also administered in the study. The AUC of the modafinil:malonic acid co-crystal was determined to be 40 to 60 percent higher than that of the pure modafinil. Such a higher bioavailability illustrates the modulation of an important pharmacokinetic parameter due to an embodiment of the present invention. A compilation of important pharmacokinetic parameters measured during the animal study are included in Table XXV.

Table XXV- Pharmacokinetic parameters of modafinil:malonic acid co-crystal and pure modafinil in dogs

Parameter	Pure Modafinil	Modafinil:malonic acid co-crystal
Median particle size	2 micrometers	16 micrometers
C_{max} (ng/mL)	11.0 ± 5.9	10.3 ± 3.4
T_{max} (hours)	1.3 ± 0.6	1.7 ± 0.6
AUC (relative)	1.0	1.4-1.6
Half-life (hours)	2.1 ± 0.7	5.1 ± 2.4

The increased half-life and bioavailability of modafinil in the malonic acid form I co-crystal may be due to the presence of malonic acid. It is believed that the malonic acid may be inhibiting one or more pathways responsible for the metabolism or elimination of modafinil. It is noted that modafinil and malonic acid share a similar structure: each including two carbonyl or sulfonyl groups separated by a $-CH_2-$ and each molecule is terminated with a group that is capable of participation in a hydrogen bond with an enzyme. Such a mechanism may take place with other APIs or co-crystal formers of similar structure.

Example 38

The stability of the modafinil:malonic acid form I co-crystal was measured at various temperatures and relative humidities over a four week period. No degradation was found to occur at 20 or 40 degrees C. At 60 degrees C, about 0.14 percent degradation per day was determined based on a simple exponential model. At 80 degrees C, about 8 percent degradation per day was determined.

TABLE I

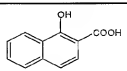
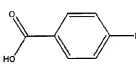
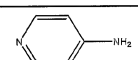
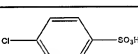
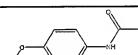
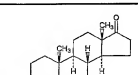
Co-Crystal Former	MW (g/mol)	MP (°C)	Class	Functionality	# acceptors	# donors	Molecular Structure	pKa Values
1-Hydroxy-2-naphthoic acid	188.18	191-192	2	Carboxylic acid, alcohol	1	2		2.7, 13.5
4-aminobenzoic acid	137.14	187-188	2	Amine, carboxylic acid	1	3		4.7, 4.8
4-aminopyridine	94.11	158-159	3	Amine, pyridine	1	2		10
4-Chlorobenzene-sulfonic acid	192.63	67	1	SO_3H	3	1		0-1
4-ethoxyphenyl urea	180.2	173-174	3	Amide, NH	2	3		~7-9
7-oxo-DHEA	303	190-192	1	Alcohol, Ketone	3	1		

TABLE I

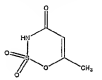
Co-Crystal Former	MW (g/mol)	MP (°C)	Class	Functionality	# acceptors	# donors	Molecular Strucutre	pKa Values
Acesulfame	163.15	123-124	3	SO_2, Amide	4	1		~5-7
Acetohydroxamic acid	75.07	89-92	3	Amide, NH, OH	2	2		8.7
Adenine	135.13	220 (sub.)	1	Amine, NH	3	3		3.8
Adipic Acid	146.14	152	1	Carboxylic acid	2	2	$HOOC(CH_2)_4COOH$	4.44, 5.44
Alanine	89.09	289-291	1	Amine, carboxillic acid	1	3		2.35, 9.87
Allopurinaol	136.11	>350	3	OH, NH	4	2		10.2

TABLE I

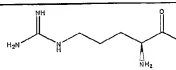
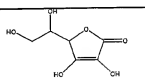
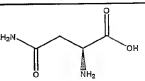
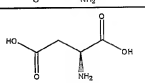
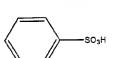
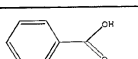
Co-Crystal Former	MW (g/mol)	MP (°C)	Class	Functionality	# acceptors	# donors	Molecular Strucutre	pKa Values
Arginine	174.2	244 (dec.)	1	Amine, COOH	2	7		2.18, 9.09, 13.2
Ascorbic acid	176.12	190-192	1	C=O, OH	6	4		4.17, 11.57
Asparagine	132.12	234-235	1	Amine, amide, COOH	3	5		2.02, 8.5
Aspartic acid	133.1	270-271	1	Amine, COOH	2	4		1.88, 3.65, 9.60
Benzenesulfonic Acid	158.18	43-44	1	SO_3H	2	1		0.70, 1.58
Benzoic acid*	122.12	122-123	2	COOH	1	1		4.19

TABLE I

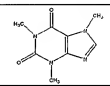
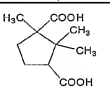
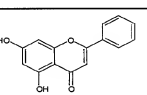
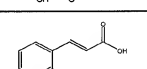
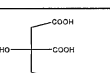
Co-Crystal Former	MW (g/mol)	MP (°C)	Class	Functionality	# acceptors	# donors	Molecular Structure	pKa Values
Caffeine	194.19	238	3	C=O	3	0		
Camphoric acid	200.23	186-189	2	Carboxylic acid	2	2		4.72, 5.83
Capric acid	172.27	31.4	1	Carboxylic acid	1	1	$CH_3(CH_2)_8COOH$	4.9
Chrysin	254.24	285	1	Phenol, ether, ketone	2	2		
Cinnamic acid	144.2	133	3	Carboxylic acid	1	1		4.4
Citric Acid	192.12	153	1	OH, COOH	4	4		3.13, 4.76, 6.40

TABLE I

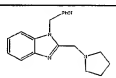
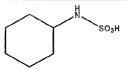
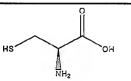
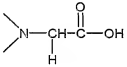
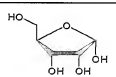
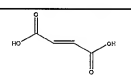
Co-Crystal Former	MW (g/mol)	MP (°C)	Class	Functionality	# acceptors	# donors	Molecular Strucutre	pKa Values
Clemizole	325.84	167	1	Pyrrolidine	3	0		
Cyclamic acid	179.24	169-170	3	NH, SO_3H	2	2		-2
Cysteine	121.15	---	1	Amine, COOH, SH	2	4		1.71, 8.33, 10.78
Dimethylglycine	103.1	178-192	1	Amine, Carboxylic acid	2	1		2.5
D-Ribose	150.13	87	1	Alcohol, ether	1	4		
Fumaric acid	116.07	287	1	COOH	2	2		3.03, 4.38

TABLE I

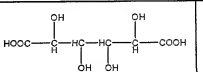
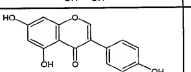
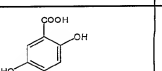
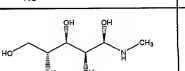
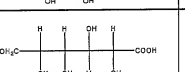
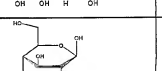
Co-Crystal Former	MW (g/mol)	MP (°C)	Class	Functionality	# acceptors	# donors	Molecular Structure	pKa Values
Galactaric acid	210.14	255 (dec)	1	Carboxylic acid, alcohol	2	6		3.08, 3.63
Genistein	270.24	297-298	1	Alcohol, Phenol, ether, ketone	2	3		
Gentisic acid	154.12	199-200 form I, 205 form II	2	Carboxylic acid, alcohol, phenol	1	3		2.93
Glucamine, N-Methyl	195.22	128-129	1	Alcohol, Amine	5	6		8.03(B)
Gluconic acid	196.15	131	1	OH, COOH	6	6		3.76
Glucosamine	179.17	88	1	OH	5	6		6.91

TABLE I

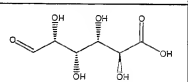
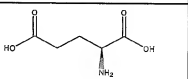
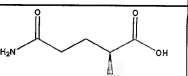
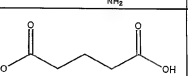
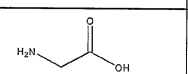
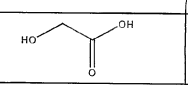
Co-Crystal Former	MW (g/mol)	MP (°C)	Class	Functionality	# acceptors	# donors	Molecular Strucutre	pKa Values
Glucuronic acid	194.14	165	1	Carboxylic acid, alcohol, aldehyde	2	5		3.18
Glutamic acid	147.13	160	1	Amine, COOH	2	4		2.19, 4.25, 9.67
Glutamine	146.15	185-186	1	Amine, Amide, COOH	2	5		2.17, 9.13
Glutaric acid	132.11	98-98	1	COOH	2	2		2.7, 4.5
Glycine	75.07	182	1	Amine, COOH	2	3		2.34, 9.6
Glycolic acid	76.05	80	1	OH, COOH	2	2		3.82

TABLE I

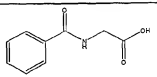
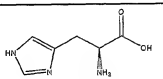
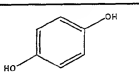
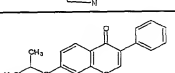
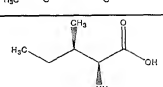
Co-Crystal Former	MW (g/mol)	MP (°C)	Class	Functionality	# acceptors	# donors	Molecular Strucutre	pKa Values
Hippuric acid	179.17	187-188	1	Amide, NH, COOH	2	2		3.55
Histidine	155.16	287 (dec.)	1	Amine, COOH, Imidazole	2	4		1.78, 5.97, 8.97
Hydroquinone*	110.11	170-171	2	OH, Phenol	2	2		~10
Imidazole	68.08	90-91	1	NH	1	1		6.92
Ipriflavone	280.32	115-117	1	Ketone, ether	3	0		
Isoleucine	131.17	168-170 (sub.)	1	Amine, COOH	1	3		2.32, 9.76

TABLE I

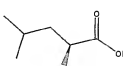
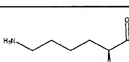
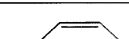
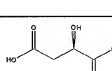
Co-Crystal Former	MW (g/mol)	MP (°C)	Class	Functionality	# acceptors	# donors	Molecular Strucutre	pKa Values
Lactobionic acid	358.3	128-130	2	Alcohol, carboxylic acid, ether	1	9		3.2
Lauric acid	200.32	44-48	1	Carboxylic acid	1	1	$CH_3(CH_2)_{10}COOH$	~4.5
Leucine	131.17	145-148 (sub.)	1	Carboxylic acid, amine	1	3		2.36, 9.6
Lysine	146.19	225 (dec.)	1	Amine, COOH	1	5		2.2, 8.9, 10.28
Maleic	116.07	138-139	1	COOH	2	2		1.92, 6.23
Malic acid	134.09	131-132	1	OH, COOH	3	3		3.46, 5.1

TABLE I

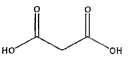
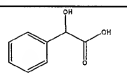
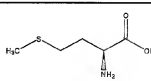
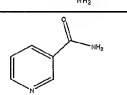
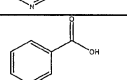
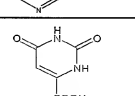
Co-Crystal Former	MW (g/mol)	MP (°C)	Class	Functionality	# acceptors	# donors	Molecular Strucutre	pKa Values
Malonic	104.06	135	1	COOH	2	2		2.83, 5.70
Mandelic acid	152.15	119	1	OH, COOH	2	2		3.37
Methionine	149.21	280-282 (dec.)	1	Amine, COOH, S-Me	2	3		2-3, 9
Nicotinamide	122.12	128-131	1	Pyridine, amide	2	2		3.3
Nicotinic acid	123.11	236-237	2	Carboxylic acid, pyridine	2	1		2.07(B), 4.85
Orotic acid	156.1	345-346	2	Carboxilic acid, lactam	3	3		5.85, 8.95

TABLE I

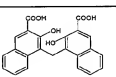
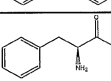
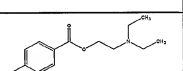
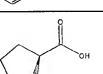
Co-Crystal Former	MW (g/mol)	MP (°C)	Class	Functionality	# acceptors	# donors	Molecular Strucutre	pKa Values
Oxalic acid	90.04	189 (dec)	2	Carboxilic acid	2	2		1.27, 4.27
Palmitic acid	256.43	63-64	1	Carboxylic acid	1	1	$CH_3(CH_2)_{14}COOH$	4.9
Pamoic	388.38	280 (dec)	2	Carboxylic acid, phenol	2	4		2.51, 3.1
Phenylalanine	165.19	283 (dec.)	1	Amine, COOH	1	3		~2, ~9
Piperazine	86.14	106	1	NH	0	2		9.82(B)
Procaine	236.31	61	1	Amine, C=O	2	2		8.9(B)
Proline	115.13	220-222 (dec.)	1	COOH, NH	1	2		1.99, 10.6

TABLE I

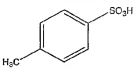
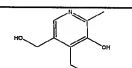
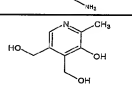
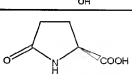
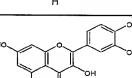
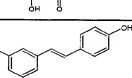
Co-Crystal Former	MW (g/mol)	MP (°C)	Class	Functionality	# acceptors	# donors	Molecular Strucutre	pKa Values
p-Toluenesulfonic acid	172.2	106-107	2	Sulfonic acid	2	1		-1.34
Pyridoxamine	168	193-194	2	OH, Amine, Pyridine	3	4		~9
Pyridoxine	170	160	2	Alcohol, Pyridine	3	3		~9
Pyroglutamic acid	129.12	162	2	Carboxylic acid, Lactam	2	2		3.32
Quercetin	302.24	314 dec.	1	Phenol, ether, ketone	2	5		
Resveratrol	228.24	253-255	1	Phenol	0	3		

TABLE I

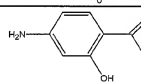
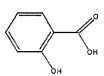
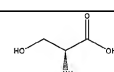
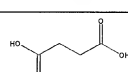
Co-Crystal Former	MW (g/mol)	MP (°C)	Class	Functionality	# acceptors	# donors	Molecular Strucutre	pKa Values
Saccharin	183.19	228-230	1	Amide, C=O, S=O, N-H	3	1		2
Salicylic acid, 4-amino	153.14	150-151	3	COOH, OH, Analine	1	4		3.25, 10, 3.5(B)
Salicylic acid	138.12	159	3	COOH, OH	2	2		2.98, 13.82
Sebacic acid	202.25	134.5	1	Carboxylic acid	2	2	$HOOC(CH_2)_8COOH$	4.59, 5.59
Serine	105.09	228 (dec.)	1	Carboxylic acid, amine, OH	2	3		2.21, 9.15
Stearic acid	284.47	70-71	1	Carboxylic acid	1	1	$CH_3(CH_2)_{16}COOH$	4.9
Succinic acid	118.09	185-187	1	Carboxylic acid	2	2		4.21, 5.64

TABLE I

Co-Crystal Former	MW (g/mol)	MP (°C)	Class	Functionality	# acceptors	# donors	Molecular Structure	pKa Values
Tartaric acid	150.09	205-206	1	Carboxylic acid	4	4		3.02, 4.36
Threonine	119.12	255-257 (dec.)	1	Amine, COOH, OH	2	4		2.15, 9.12
TRIS	121.13	171-172	2	Amine, OH	3	5		5.91, 8.3
Tryptophan	204.23	289 (dec.)	1	Amine, COOH, Indole	1	4		2.38, 9.39
Tyrosine	181.19	342-344	1	Amine, COOH, OH	2	3		2.2, 9.11, 10.07
Urea	60.06	Dec.	1	C=O, NH2	1	4		~8

TABLE I

Co-Crystal Former	MW (g/mol)	MP (°C)	Class	Functionality	# acceptors	# donors	Molecular Structure	pKa Values
Valine	117.15	315	1	Amine, COOH	1	3		~4.5, ~9
Vitamin K5	209.68	280-282 (dec.)	3	Amine, OH	1	3		~9
Xylitol	152.15	93-95 (I)	2	OH	5	5		~9

TABLE II

Co-crystal Former	Co-crystal Former Functional Group	Interacting Group						
1,5-Napthalene-disulfonic Acid	Sulfonic Acid	pyridine	ketone	aldehyde	ether	ester	amide	Carboxylic Acid
1-Hydroxy-2-naphthoic acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	aniline	phenol
1-Hydroxy-2-naphthoic acid	alcohol	alcohol	ketone	thiol	amide	amine	aniline	phenol
4-Aminobenzoic Acid	Amine	alcohol	ketone	thiol	amide	amine	aniline	phenol
4-Aminobenzoic Acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	aniline	phenol
4-aminopyridine	Amine	alcohol	ketone	thiol	amide	amine	aniline	phenol
4-aminopyridine	Pyridine	*alcohol	pyridinium	*	*amide	nitro	*amine	*Carboxylic Acid
4-Chlorobenzene-Sulfonic Acid	Sulfonic Acid	pyridine	ketone	aldehyde	ether	ester	amide	Carboxylic Acid
4-ethoxyphenyl Urea	Amide	alcohol	ketone	thiol	amide	amine	aniline	phenol
4-ethoxyphenyl Urea	Amine	alcohol	ketone	thiol	amide	amine	aniline	phenol
7-oxo-DHEA	alcohol	alcohol	ketone	thiol	amide	amine	aniline	phenol
7-oxo-DHEA	Ketone	alcohol		thiol	amide	amine	aniline	phenol
Acesulfame	Sulfone	pyridine	ketone	aldehyde	ether	ester	amide	carboxilic acid
Acesulfame	Amide	alcohol	ketone	thiol	amide	amine	aniline	phenol
Acetohydroxamic Acid	Amide	alcohol	ketone	thiol	amide	amine	aniline	phenol
Acetohydroxamic Acid	Amine	alcohol	ketone	thiol	amide	amine	aniline	phenol
Acetohydroxamic Acid	Alcohol	alcohol	ketone	thiol	amide	amine	aniline	phenol
Adenine	Amine	alcohol	ketone	thiol	amide	amine	aniline	phenol
Adenine	N	*alcohol	pyridinium	*	*amide	nitro	*amine	*carboxilic acid
Adipic acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	aniline	phenol
Alanine	Amine	alcohol	ketone	thiol	amide	amine	aniline	phenol
Alanine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	aniline	phenol
Allopurinol	Alcohol	alcohol	ketone	thiol	amide	amine	aniline	phenol
Allopurinol	Amine	alcohol	ketone	thiol	amide	amine	aniline	phenol
Arginine	Amine	alcohol	ketone	thiol	amide	amine	aniline	phenol
Arginine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	aniline	phenol
Ascorbic Acid	Ketone	alcohol		thiol	amide	amine	aniline	phenol
Ascorbic Acid	Alcohol	alcohol	ketone	thiol	amide	amine	aniline	phenol
Ascorbic Acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	aniline	phenol

TABLE II

Co-crystal Former									
1,5-Napthalene-disulfonic Acid	amine	metals	thioether		sulfate	alcohol			
1-Hydroxy-2-naphthoic acid	phosphate	sulfate	sulfone	nitrate	pyridine	carboxilic acid	metals		aldehyde
1-Hydroxy-2-naphthoic acid	phosphate	sulfate	sulfone	nitrate	pyridine	carboxilic acid	metals		aldehyde
4-Aminobenzoic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid		metals
4-Aminobenzoic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid		metals
4-aminopyridine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid		metals
4-aminopyridine	*sulfonamide	*ketone	ether	triazole		ammonium	oxime		*chlorine
4-Chlorobenzene-Sulfonic Acid	amine	metals	thioether		sulfate	alcohol			
4-ethoxyphenyl Urea	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid		metals
4-ethoxyphenyl Urea	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid		metals
7-oxo-DHEA	phosphate	sulfate	sulfone	nitrate	pyridine	carboxilic acid	metals		aldehyde
7-oxo-DHEA	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid		metals
Acesulfame	amine	metals	thioether		sulfate	alcohol			
Acesulfame	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid		metals
Acesulfame	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid		metals
Acetohydroxamic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid		metals
Acetohydroxamic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid		metals
Adenine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid		metals
Adenine	*sulfonamide	*ketone	ether	triazole		ammonium	oxime		*chlorine
Adipic acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid		metals
Alanine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid		metals
Alanine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid		metals
Allopurinaol	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid		metals
Allopurinaol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid		metals
Arginine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid		metals
Arginine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid		metals
Ascorbic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid		metals
Ascorbic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid		metals
Ascorbic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid		metals

TABLE II

Co-crystal Former									
1,5-Napthalene-disulfonic Acid									
1-Hydroxy-2-naphthoic acid	ester	ether	cyano		furan	bromine	chlorine	s-heterocyclic	
1-Hydroxy-2-naphthoic acid	ester	ether	cyano		furan	bromine	chlorine	s-heterocyclic	
4-Aminobenzoic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine	
4-Aminobenzoic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine	
4-aminopyridine	aldehyde	ester	ether	cyano		furan	bromine	chlorine	
4-aminopyridine		thiol	n-heterocyclic ring	thionedisulfide	pyrrolidindione	iodine	hydrazone	thiocyanate	
4-Chlorobenzene-Sulfonic Acid									
4-ethoxyphenyl Urea	aldehyde	ester	ether	cyano		furan	bromine	chlorine	
4-ethoxyphenyl Urea	aldehyde	ester	ether	cyano		furan	bromine	chlorine	
7-oxo-DHEA	ester	ether	cyano		furan	bromine	chlorine	s-heterocyclic	
7-oxo-DHEA	aldehyde	ester	ether	cyano		furan	bromine	chlorine	
Acesulfame									
Acesulfame	aldehyde	ester	ether	cyano		furan	bromine	chlorine	
Acetohydroxamic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine	
Acetohydroxamic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine	
Acetohydroxamic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine	
Adenine	aldehyde	ester	ether	cyano		furan	bromine	chlorine	
Adenine		thiol	n-heterocyclic ring	thionedisulfide	pyrrolidindione	iodine	hydrazone	thiocyanate	
Adipic acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine	
Alanine	aldehyde	ester	ether	cyano		furan	bromine	chlorine	
Alanine	aldehyde	ester	other	cyano		furan	bromine	chlorine	
Allopurinaol	aldehyde	ester	ether	cyano		furan	bromine	chlorine	
Allopurinaol	aldehyde	ester	ether	cyano		furan	bromine	chlorine	
Arginine	aldehyde	ester	ether	cyano		furan	bromine	chlorine	
Arginine	aldehyde	ester	ether	cyano		furan	bromine	chlorine	
Ascorbic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine	
Ascorbic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine	
Ascorbic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine	

TABLE II

Co-crystal Former							
1,5-Napthalene-disulfonic Acid							
1-Hydroxy-2-naphthoic acid	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		fluorine
1-Hydroxy-2-naphthoic acid	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		fluorine
4-Aminobenzoic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
4-Aminobenzoic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
4-aminopyridine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
4-aminopyridine	*bromine		hydroxamic acid	cyano	carboxamide	*sulfonic acid	*phosphoric acid
4-Chlorobenzene-Sulfonic Acid							
4-ethoxyphenyl Urea	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
4-ethoxyphenyl Urea	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
7-oxo-DHEA	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		fluorine
7-oxo-DHEA	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Acesulfame							
Acesulfame	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Acetohydroxamic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Acetohydroxamic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Acetohydroxamic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Adenine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Adenine	*bromine		hydroxamic acid	cyano	carboxamide	*sulfonic acid	*phosphoric acid
Adipic acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Alanine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Alanine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Allopurinaol	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Allopurinaol	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Arginine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Arginine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Ascorbic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Ascorbic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Ascorbic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	

TABLE II

Co-crystal Former								
1,5-Napthalene-disulfonic Acid								
1-Hydroxy-2-naphthoic acid	carbamate	imidazole	BF4					
1-Hydroxy-2-naphthoic acid	carbamate	imidazole	BF4					
4-Aminobenzoic Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
4-Aminobenzoic Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
4-aminopyridine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
4-aminopyridine	N-oxide	ester	ether	fluorine	acetate	thione	dithiadiazocyclopentadienyl	
4-Chlorobenzene-Sulfonic Acid								
4-ethoxyphenyl Urea	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
4-ethoxyphenyl Urea	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
7-oxo-DHEA	carbamate	imidazole	BF4					
7-oxo-DHEA	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Acesulfame								
Acesulfame	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Acesulfame	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Acetohydroxamic Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Acetohydroxamic Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Acetohydroxamic Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Adenine								
Adenine	N-oxide	ester	ether	fluorine	acetate	thione	dithiadiazocyclopentadienyl	
Adipic acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Alanine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Alanine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Allopurinaol	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Allopurinaol	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Arginine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Arginine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Ascorbic Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Ascorbic Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Ascorbic Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea

TABLE II

Co-crystal Former				
1,5-Naphthalene-disulfonic Acid				
1-Hydroxy-2-naphthoic acid				
1-Hydroxy-2-naphthoic acid				
4-Aminobenzoic Acid	Iodine			
4-Aminobenzoic Acid	Iodine			
4-aminopyridine	Iodine			
4-aminopyridine				
4-Chlorobenzene-Sulfonic Acid				
4-ethoxyphenyl Urea	Iodine	epoxide	peroxide	
4-ethoxyphenyl Urea	Iodine			
7-oxo-DHEA				
7-oxo-DHEA	Iodine			
Acesulfame				
Acesulfame	Iodine	epoxide	peroxide	
Acetohydroxamic Acid	Iodine	epoxide	peroxide	
Acetohydroxamic Acid	Iodine			
Acetohydroxamic Acid	Iodine	epoxide		
Adenine	Iodine			
Adenine				
Adipic acid	Iodine			
Alanine	Iodine			
Alanine	Iodine			
Allopurinol	Iodine	epoxide		
Allopurinol	Iodine			
Arginine	Iodine			
Arginine	Iodine			
Ascorbic Acid	Iodine			
Ascorbic Acid	Iodine	epoxide		
Ascorbic Acid	Iodine			

TABLE II

Co-crystal Former	Co-crystal Former Functional Group	Interacting Group					
Asparagine	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Asparagine	Amide	alcohol	ketone	thiol	amide	amine	analine	phenol
Asparagine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Aspartic Acid	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Aspartic Acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Benzenesulfonic Acid	Sulfonic Acid	pyridine	ketone	aldehyde	ether	ester	amide	Carboxylic Acid
Benzoic Acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Caffeine	Ketone	alcohol		thiol	amide	amine	analine	phenol
Camphoric acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Capric acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Genistein	Ketone	alcohol		thiol	amide	amine	analine	phenol
Genistein	Phenol	amine	amide	sulfoxide	n	pyridine	cyano	aldehyde
Genistein	Ether	aromatic-N	amide	amine	aromatic_s	Sp2 amine	sulfoxide	chlorate
Cinnamic acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Citric Acid	Alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
Citric Acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Clemizole	Pyrrolidine	*alcohol	pyridinium	*	*amide	nitro	*amine	*carboxilic acid
Cyclamic Acid	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Cyclamic Acid	Sulfonic Acid	pyridine	ketone	aldehyde	ether	ester	amide	Carboxylic Acid
Cysteine	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Cysteine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Cysteine	Thiol	carboxylic acid	sodium	aldehyde	ketone	-N	cadmium	
Dimethylglycine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Dimethylglycine	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
D-ribose	Ether	aromatic-N	amide	amine	aromatic_s	Sp2 amine	sulfoxide	chlorate
D-ribose	Alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
Fumaric Acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Galactaric acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Galactaric acid	alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
Chrysin	Ketone	alcohol		thiol	amide	amine	analine	phenol

TABLE II

Co-crystal Former									
Asparagine	phosphate	sulfate	sulfone	nitrate		pyridine		carboxilic acid	metals
Asparagine	phosphate	sulfate	sulfone	nitrate		pyridine		Carboxylic Acid	metals
Asparagine	phosphate	sulfate	sulfone	nitrate		pyridine		carboxilic acid	metals
Aspartic Acid	phosphate	sulfate	sulfone	nitrate		pyridine		carboxilic acid	metals
Aspartic Acid	phosphate	sulfate	sulfone	nitrate		pyridine		carboxilic acid	metals
Benzenesulfonic Acid	amine	metals	thioether			sulfate	alcohol		
Benzoic Acid	phosphate	sulfate	sulfone	nitrate		pyridine		carboxilic acid	metals
Caffeine	phosphate	sulfate	sulfone	nitrate		pyridine		Carboxylic Acid	metals
Camphoric acid	phosphate	sulfate	sulfone	nitrate		pyridine		carboxilic acid	metals
Capric acid	phosphate	sulfate	sulfone	nitrate		pyridine		carboxilic acid	metals
Genistein	phosphate	sulfate	sulfone	nitrate		pyridine		Carboxylic Acid	metals
Genistein		alchohol		ester		ether	n-oxide	chlorine	fluorine
Genistein	chlorine		cyano	ester		amine	nitro	nitrate	bromine
Cinnamic acid	phosphate	sulfate	sulfone	nitrate		pyridine		carboxilic acid	metals
Citric Acid	phosphate	sulfate	sulfone	nitrate		pyridine		Carboxylic Acid	metals
Citric Acid	phosphate	sulfate	sulfone	nitrate		pyridine		carboxilic acid	metals
Clemizole	*sulfonamide	*ketone	ether	triazole			ammonium	oxime	*chlorine
Cyclamic Acid	phosphate	sulfate	sulfone	nitrate		pyridine		carboxilic acid	metals
Cyclamic Acid	amine	metals	thioether			sulfate	alcohol		
Cysteine	phosphate	sulfate	sulfone	nitrate		pyridine		carboxilic acid	metals
Cysteine	phosphate	sulfate	sulfone	nitrate		pyridine		carboxilic acid	metals
Cysteine	arsenic	chlorine	alcohol	potassium		Ru		Rb	Sb
Dimethylglycine	phosphate	sulfate	sulfone	nitrate		pyridine		carboxilic acid	metals
Dimethylglycine	phosphate	sulfate	sulfone	nitrate		pyridine		carboxilic acid	metals
D-ribose	chlorine		cyano	ester		amine	nitro	nitrate	bromine
D-ribose	phosphate	sulfate	sulfone	nitrate		pyridine		Carboxylic Acid	metals
Fumaric Acid	phosphate	sulfate	sulfone	nitrate		pyridine		carboxilic acid	metals
Galactaric acid	phosphate	sulfate	sulfone	nitrate		pyridine		carboxilic acid	metals
Galactaric acid	phosphate	sulfate	sulfone	nitrate		pyridine	carboxilic acid	metals	aldehyde
Chrysin	phosphate	sulfate	sulfone	nitrate		pyridine		Carboxylic Acid	metals

TABLE II

Co-crystal Former									
Asperagine	aldehyde	ester	ether	cyano			furan	bromine	chlorine
Asperagine	aldehyde	ester	ether	cyano			furan	bromine	chlorine
Asperagine	aldehyde	ester	ether	cyano			furan	bromine	chlorine
Aspartic Acid	aldehyde	ester	ether	cyano			furan	bromine	chlorine
Aspartic Acid	aldehyde	ester	ether	cyano			furan	bromine	chlorine
Benzenesulfonic Acid									
Benzoic Acid	aldehyde	ester	ether	cyano			furan	bromine	chlorine
Caffeine	aldehyde	ester	ether	cyano			furan	bromine	chlorine
Camphoric acid	aldehyde	ester	ether	cyano			furan	bromine	chlorine
Capric acid	aldehyde	ester	ether	cyano			furan	bromine	chlorine
Genistein	aldehyde	ester	ether	cyano			furan	bromine	chlorine
Genistein	bromine	iodine	ketone	sulfonic acid	sulfate	phosphate	phosphonic acid	carboxylic acid	
Genistein	aldehyde	ketone	peroxide	epoxide			heterocyclic-S	iodine	
Cinnamic acid	aldehyde	ester	ether	cyano			furan	bromine	chlorine
Citric Acid	aldehyde	ester	ether	cyano			furan	bromine	chlorine
Citric Acid	aldehyde	ester	ether	cyano			furan	bromine	chlorine
		thiol	n-heterocyclic ring	thionedisulfide	pyrrolidindione	iodine	hydrazone	thiocyanate	
Clemizole	aldehyde	ester	ether	cyano			furan	bromine	chlorine
Cyclamic Acid									
Cyclamic Acid									
Cysteine	aldehyde	ester	ether	cyano			furan	bromine	chlorine
Cysteine	aldehyde	ester	ether	cyano			furan	bromine	chlorine
Cysteine									
Dimethylglycine	aldehyde	ester	ether	cyano			furan	bromine	chlorine
Dimethylglycine	aldehyde	ester	ether	cyano			furan	bromine	chlorine
D-ribose	aldehyde	ketone	peroxide	epoxide			heterocyclic-S	iodine	
D-ribose	aldehyde	ester	ether	cyano			furan	bromine	chlorine
Fumaric Acid	aldehyde	ester	ether	cyano			furan	bromine	chlorine
Galactaric acid	aldehyde	ester	ether	cyano			furan	bromine	chlorine
Galactaric acid	ester	ether	cyano		furan	bromine	chlorine	s-heterocyclic	
Chrysin	aldehyde	ester	ether	cyano			furan	bromine	chlorine

TABLE II

Co-crystal Former							
Asparagine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Asparagine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Asparagine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Aspartic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Aspartic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Benzenesulfonic Acid							
Benzoic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Caffeine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Camphoric acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Capric acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Genistein	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Genistein	nitro	sulfone	analine				
Genistein	ester	ether	carboxylic acid	sulfate	sulfone		alcohol
Cinnamic acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Citric Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Citric Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Clemizole	*bromine		hydroxamic acid	cyano	carboxamide	*sulfonic acid	*phosphoric acid
Cyclamic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Cyclamic Acid							
Cysteine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Cysteine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Cysteine							
Dimethylglycine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Dimethylglycine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
D-ribose	ester	ether	carboxylic acid	sulfate	sulfone		alcohol
D-ribose	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Fumaric Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Galactaric acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Galactaric acid	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		fluorine
Chrysin	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	

TABLE II

Co-crystal Former								
Asparagine	fluorine	carbamate	imidazole	BF4			N-SO2	
Asparagine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Asparagine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Aspartic Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Aspartic Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Benzenesulfonic Acid								
Benzoic Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Caffeine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Camphoric acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Capric acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Genistein	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Genistein	fluorine	carbamate	imidazole	BF4			N-SO2	*thiourea*
Genistein								
Genistein		phosphate	cyanamide					
Cinnamic acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Citric Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Citric Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Clemizole	N-oxide	ester	ether	fluorine	acetate	thione	dithiadiazocyclopentadienyl	
Cyclamic Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Cyclamic Acid								
Cysteine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Cysteine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Cysteine								
Dimethylglycine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Dimethylglycine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
D-ribose		phosphate	cyanamide					
D-ribose	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Fumaric Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Galactaric acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Galactaric acid	carbamate	imidazole	BF4					
Chrysin	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea

TABLE II

Co-crystal Former			
Asparagine	Iodine		
Asparagine	Iodine	epoxide	peroxide
Asparagine	Iodine		
Aspartic Acid	Iodine		
Aspartic Acid	Iodine		
Benzenesulfonic Acid			
Benzoic Acid	Iodine		
Caffeine	Iodine		
Camphoric acid	Iodine		
Capric acid	Iodine		
Genistein	Iodine		
Genistein			
Genistein			
Cinnamic acid	Iodine		
Citric Acid	Iodine	epoxide	
Citric Acid	Iodine		
Clemizole			
Cyclamic Acid	Iodine		
Cyclamic Acid			
Cysteine	Iodine		
Cysteine	Iodine		
Cysteine			
Dimethylglycine	Iodine		
Dimethylglycine	Iodine		
D-ribose			
D-ribose	Iodine	epoxide	
Fumaric Acid	Iodine		
Galactaric acid	Iodine		
Galactaric acid			
Chrysin	Iodine		

TABLE II

Co-crystal Former	Co-crystal Former Functional Group	Interacting Group							
Chrysin	Phenol	amine	amide	sulfoxide	n	pyridine	cyano	aldehyde	
Chrysin	Ether	aromatic-N	amide	amine	aromatic_s	Sp2 amine	sulfoxide	chlorate	
Gentisic acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol	
Gentisic acid	Phenol	amine	amide	sulfoxide	n	pyridine	cyano	aldehyde	
Glucamine, N-methyl	alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol	
Glucamine, N-methyl	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol	
Gluconic Acid	Alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol	
Gluconic Acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol	
Glucosamine	alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol	
Glucuronic acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol	
Glucuronic acid	alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol	
Glucuronic acid	Aldehyde	alcohol	ketone	thiol	amide	amine	analine	phenol	
Glutamic Acid	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol	
Glutamic Acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol	
Glutamine	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol	
Glutamine	Amide	alcohol	ketone	thiol	amide	amine	analine	phenol	
Glutamine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol	
Glutaric Acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol	
Glycine	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol	
Glycine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol	
Glycolic Acid	Alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol	
Glycolic Acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol	
Hippuric Acid	Amide	alcohol	ketone	thiol	amide	amine	analine	phenol	
Hippuric Acid	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol	
Hippuric Acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol	
Histidine	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol	
Histidine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol	
Histidine	Imidazole	Imidazole	chlorine	acetamide	carboxylate		thione	nitro	
Hydroquinone	Alcohol	alcohol	Ketone	thiol	amide	amine	analine	phenol	
Hydroquinone	Phenol	amine	amide	sulfoxide	n	pyridine	cyano	aldehyde	
Imidazole	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol	

TABLE II

Co-crystal Former								
Chrysin		alchohol		ester	ether	n-oxide	chlorine	fluorine
Chrysin	chlorine		cyano	ester	amine	nitro	nitrate	bromine
Gentisic acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Gentisic acid		alchohol		ester	ether	n-oxide	chlorine	fluorine
Glucamine, N-methyl	phosphate	sulfate	sulfone	nitrate	pyridine	carboxilic acid	metals	aldehyde
Glucamine, N-methyl	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Gluconic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Gluconic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Glucosamine	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Glucuronic acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Glucuronic acid	phosphate	sulfate	sulfone	nitrate	pyridine	carboxilic acid	metals	aldehyde
Glucuronic acid	phosphate	sulfate	sulfone	nitrate	pyridine	aromatic	carboxilic acid	metals
Glutamic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Glutamic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Glutamine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Glutamine	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Glutamine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Glutaric Acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Glycine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Glycine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Glycolic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Glycolic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Hippuric Acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Hippuric Acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Hippuric Acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Histidine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Histidine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Histidine	cyanamide	ketone	cyano	Carboxylic Acid	alcohol		thiol	amine
Hydroquinone	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Hydroquinone		alchohol		ester	ether	n-oxide	chlorine	fluorine
Imidazole	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals

TABLE II

Co-crystal Former									
Chrysin	bromine	iodine	ketone	sulfonic acid	sulfate	phosphate	phosphonic acid	carboxylic acid	
Chrysin	aldehyde	ketone	peroxide	epoxide			heterocyclic-S	iodine	
Gentisic acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine	
Gentisic acid	bromine	iodine	ketone	sulfonic acid	sulfate	phosphate	phosphonic acid	carboxylic acid	
Glucamine, N-methyl	ester	ether	cyano		furan	bromine	chlorine	s-heterocyclic	
Glucamine, N-methyl	aldehyde	ester	ether	cyano		furan	bromine	chlorine	
Gluconic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine	
Gluconic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine	
Glucosamine	aldehyde	ester	ether	cyano		furan	bromine	chlorine	
Glucuronic acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine	
Glucuronic acid	ester	ether	cyano		furan	bromine	chlorine	s-heterocyclic	
Glucuronic acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine	
Glutamic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine	
Glutamic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine	
Glutamine	aldehyde	ester	ether	cyano		furan	bromine	chlorine	
Glutamine	aldehyde	ester	ether	cyano		furan	bromine	chlorine	
Glutamine	aldehyde	ester	ether	cyano		furan	bromine	chlorine	
Glutaric Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine	
Glycine	aldehyde	ester	ether	cyano		furan	bromine	chlorine	
Glycine	aldehyde	ester	ether	cyano		furan	bromine	chlorine	
Glycolic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine	
Glycolic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine	
Hippuric Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine	
Hippuric Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine	
Hippuric Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine	
Histidine	aldehyde	ester	ether	cyano		furan	bromine	chlorine	
Histidine	aldehyde	ester	ether	cyano		furan	bromine	chlorine	
Histidine	phosphinic acid hemihydrate	chlorine	sulfonyl	sulfoxide	amide	fluorine	sulfonate ester		
Hydroquinone	aldehyde	ester	ether	cyano		furan	bromine	chlorine	
Hydroquinone	bromine	iodine	ketone	sulfonic acid	sulfate	phosphate	phosphonic acid	carboxylic acid	
Imidazole	aldehyde	ester	ether	cyano		furan	bromine	chlorine	

TABLE II

Co-crystal Former								
Chrysin	nitro	sulfone	analine					
Chrysin	ester	ether	carboxylic acid	sulfate	sulfone			alcohol
Gentisic acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		
Gentisic acid	nitro	sulfone	analine					
Glucamine, N-methyl	pyridine	cyano	n-heterocyclic	ketone	phosphate ester			fluorine
Glucamine, N-methyl	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		
Gluconic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		
Gluconic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		
Glucosamine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		
Glucuronic acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		
Glucuronic acid	pyridine	cyano	n-heterocyclic	ketone	phosphate ester			fluorine
Glucuronic acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		
Glutamic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		
Glutamic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		
Glutamine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		
Glutamine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		
Glutamine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		
Glutaric Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		
Glycine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		
Glycine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		
Glycolic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		
Glycolic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		
Hippuric Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		
Hippuric Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		
Hippuric Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		
Histidine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		
Histidine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		
Histidine								
Hydroquinone	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		
Hydroquinone	nitro	sulfone	analine					
Imidazole	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		

TABLE II

Co-crystal Former								
Chrysin								
Chrysin		phosphate	cyanamide					
Gentisic acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Gentisic acid								
Glucamine, N-methyl	carbamate	imidazole	BF4					
Glucamine, N-methyl	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Gluconic Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Gluconic Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Glucosamine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Glucuronic acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Glucuronic acid	carbamate	imidazole	BF4					
Glucuronic acid	fluorine	carbamate	imidazole	BF4	alkane	aromatic	N-SO2	thiourea
Glutamic Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Glutamic Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Glutamine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Glutamine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Glutamine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Glutaric Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Glycine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Glycine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Glycolic Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Glycolic Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Hippuric Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Hippuric Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Hippuric Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Histidine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Histidine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Histidine								
Hydroquinone	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Hydroquinone								
Imidazole	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea

TABLE II

Co-crystal Former			
Chrysin			
Chrysin			
Gentisic acid	iodine		
Gentisic acid			
Glucamine, N-methyl			
Glucamine, N-methyl	iodine		
Gluconic Acid	iodine	epoxide	
Gluconic Acid	iodine		
Glucosamine	iodine	epoxide	
Glucuronic acid	iodine		
Glucuronic acid			
Glucuronic acid	iodine	epoxide	
Glutamic Acid	iodine		
Glutamic Acid	iodine		
Glutamine	iodine		
Glutamine	iodine	epoxide	peroxide
Glutamine	iodine		
Glutaric Acid	iodine		
Glycine	iodine		
Glycine	iodine		
Glycolic Acid	iodine	epoxide	
Glycolic Acid	iodine		
Hippuric Acid	iodine	epoxide	peroxide
Hippuric Acid	iodine		
Hippuric Acid	iodine		
Histidine	iodine		
Histidine	iodine		
Histidine	iodine		
Hydroquinone	iodine	epoxide	
Hydroquinone	iodine		
Imidazole	iodine		

TABLE II

Co-crystal Former	Co-crystal Former Functional Group	Interacting Group						
Ipriflavone	Ether	aromatic-N	amide	amine	aromatic_s	Sp2 amine	sulfoxide	chlorate
Ipriflavone	Ketone	alcohol		thiol	amide	amine	analine	phenol
Isoleucine	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Isoleucine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
lactobionic acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Lactobionic acid	alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
Lactobionic acid	Ether	aromatic-N	amide	amine	aromatic_s	Sp2 amine	sulfoxide	chlorate
Lauric acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Leucine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Leucine	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Lysine	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Lysine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Maleic	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Malic Acid	Alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
Malic Acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Maleic	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Mandelic Acid	Alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
Mandelic Acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Methionine	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Methionine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Methionine	Thioether	-N	amide	amine	_s	Sp2 amine	sulfoxide	chlorate
Nicotinamide	Pyridine	*alcohol		*	*amide	nitro	*amine	*Carboxylic Acid
Nicotinamide	Amide	alcohol	ketone	thiol	amide	amine	analine	phenol
Nicotinic Acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Nicotinic Acid	Pyridine	*alcohol		*	*amide	nitro	*amine	*Carboxylic Acid
Orotic acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Orotic acid	Lactam	alcohol	ketone	thiol	amide	amine	analine	phenol
Oxalic acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Palmitic acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Pamoic acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Pamoic acid	alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
Pamoic acid	Phenol	amine	amide	sulfoxide	n	pyridine	cyano	aldehyde

TABLE II

Co-crystal Former								
Ipriflavone	chlorine		cyano	ester	amine	nitro	nitrate	bromine
Ipriflavone	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Isoleucine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxylic acid	metals
Isoleucine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxylic acid	metals
lactobionic acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxylic acid	metals
Lactobionic acid	phosphate	sulfate	sulfone	nitrate	pyridine	carboxylic acid	metals	aldehyde
Lactobionic acid	chlorine		cyano	ester	amine	nitro	nitrate	bromine
Lauric acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxylic acid	
Leucine	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Leucine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxylic acid	metals
Lysine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxylic acid	metals
Lysine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxylic acid	metals
Maleic	phosphate	sulfate	sulfone	nitrate	pyridine		carboxylic acid	metals
Malic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Malic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxylic acid	metals
Malonic	phosphate	sulfate	sulfone	nitrate	pyridine		carboxylic acid	metals
Mandelic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Mandelic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxylic acid	metals
Methionine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxylic acid	metals
Methionine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxylic acid	metals
Methionine	chlorine		cyano	ester	amine	nitro	nitrate	bromine
Nicotinamide	*sulfonamide	*ketone	ether	triazole		ammonium	oxime	*chlorine
Nicotinamide	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Nicotinic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Nicotinic Acid	*sulfonamide	*ketone	ether	triazole		ammonium	oxime	*chlorine
Orotic acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxylic acid	
Orotic acid	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Oxalic acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxylic acid	
Palmitic acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxylic acid	
Pamoic acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxylic acid	
Pamoic acid	phosphate	sulfate	sulfone	nitrate	pyridine	carboxylic acid	metals	aldehyde
Pamoic acid		alcohol		ester	ether	n-oxide	chlorine	fluorine

TABLE II

Co-crystal Former								
ipriflavone	aldehyde	ketone	peroxide	epoxide			heterocyclic-S	iodine
ipriflavone	aldehyde	ester	ether	cyano		furan	bromine	chlorine
isoleucine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
isoleucine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
lactobionic acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Lactobionic acid	ester	ether	cyano		furan	bromine	chlorine	s-heterocyclic
Lactobionic acid	aldehyde	ketone	peroxide	epoxide			heterocyclic-S	iodine
Lauric acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Leucine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Leucine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Lysine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Lysine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Maleic	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Malic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Malic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Malonic	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Mandelic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Mandelic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Methionine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Methionine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Methionine	aldehyde	ketone	peroxide	epoxide	Ag	Se	heterocyclic-S	iodine
Nicotinamide		thiol	n-heterocyclic ring	thionedisulfide	pyrrolidindione	iodine	hydrazone	thiocyanate
Nicotinamide	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Nicotinic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Nicotinic Acid		thiol	n-heterocyclic ring	thionedisulfide	pyrrolidindione	iodine	hydrazone	thiocyanate
Orotic acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Orotic acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Oxalic acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Palmitic acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Pamoic acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Pamoic acid	ester	ether	cyano		furan	bromine	chlorine	s-heterocyclic
Pamoic acid	bromine	iodine	ketone	sulfonic acid	sulfate	phosphate	phosphonic acid	carboxylic acid

TABLE II

Co-crystal Former							
Ipriflavone	ester	ether	carboxylic acid	sulfate	sulfone		alcohol
Ipriflavone	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Isoleucine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Isoleucine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
lactobionic acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Lactobionic acid	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		fluorine
Lactobionic acid	ester	ether	carboxylic acid	sulfate	sulfone		alcohol
Lauric acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Leucine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Leucine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Lysine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Lysine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Maleic	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Malic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Malic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Melonic	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Mandelic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Mandelic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Methionine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Methionine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Methionine	ester	ether	carboxylic acid	sulfate	sulfone		alcohol
Nicotinamide	*bromine		hydroxamic acid	cyano	carboxamide	*sulfonic acid	*phosphoric acid
Nicotinamide	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Nicotinic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Nicotinic Acid	*bromine		hydroxamic acid	cyano	carboxamide	*sulfonic acid	*phosphoric acid
Orotic acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Orotic acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Oxalic acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Palmitic acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Pamoic acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Pamoic acid	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		fluorine
Pamoic acid	nitro	sulfone	aniline				

TABLE II

Co-crystal Former									
Ipriflavone									
Ipriflavone		phosphate	cyanamide						
Ipriflavone	fluorine	carbamate	imidazole	BF4				N-SO2	thiourea
Isoleucine	fluorine	carbamate	imidazole	BF4				N-SO2	thiourea
Isoleucine	fluorine	carbamate	imidazole	BF4				N-SO2	thiourea
lactobionic acid	fluorine	carbamate	imidazole	BF4				N-SO2	thiourea
Lactobionic acid	carbamate	imidazole	BF4						
Lactobionic acid		phosphate	cyanamide						
Lauric acid	fluorine	carbamate	imidazole	BF4				N-SO2	thiourea
Leucine	fluorine	carbamate	imidazole	BF4				N-SO2	thiourea
Leucine	fluorine	carbamate	imidazole	BF4				N-SO2	thiourea
Lysine	fluorine	carbamate	imidazole	BF4				N-SO2	thiourea
Lysine	fluorine	carbamate	imidazole	BF4				N-SO2	thiourea
Maleic	fluorine	carbamate	imidazole	BF4				N-SO2	thiourea
Malic Acid	fluorine	carbamate	imidazole	BF4				N-SO2	thiourea
Malic Acid	fluorine	carbamate	imidazole	BF4				N-SO2	thiourea
Malonic	fluorine	carbamate	imidazole	BF4				N-SO2	thiourea
Mandelic Acid	fluorine	carbamate	imidazole	BF4				N-SO2	thiourea
Mandelic Acid	fluorine	carbamate	imidazole	BF4				N-SO2	thiourea
Methionine	fluorine	carbamate	imidazole	BF4				N-SO2	thiourea
Methionine	fluorine	carbamate	imidazole	BF4				N-SO2	thiourea
Methionine		phosphate							
	N-oxide	ester	ether	fluorine	acetate	thione	dithiadiazocyclopentadienyl		
Nicotinamide	fluorine	carbamate	imidazole	BF4				N-SO2	thiourea
Nicotinic Acid	fluorine	carbamate	imidazole	BF4				N-SO2	thiourea
	N-oxide	ester	ether	fluorine	acetate	thione	dithiadiazocyclopentadienyl		
Nicotinic Acid	fluorine	carbamate	imidazole	BF4				N-SO2	thiourea
Orotic acid	fluorine	carbamate	imidazole	BF4				N-SO2	thiourea
Oxalic acid	fluorine	carbamate	imidazole	BF4				N-SO2	thiourea
Palmitic acid	fluorine	carbamate	imidazole	BF4				N-SO2	thiourea
Pamoic acid	fluorine	carbamate	imidazole	BF4				N-SO2	thiourea
Pamoic acid	carbamate	imidazole	BF4						
Pamoic acid									

TABLE II

Co-crystal Former			
Ipriflavone			
Ipriflavone	Iodine		
Isoleucine	Iodine		
Isoleucine	Iodine		
lactobionic acid	Iodine		
Lactobionic acid			
Lactobionic acid			
Lauric acid	Iodine		
Leucine	Iodine		
Leucine	Iodine		
Lysine	Iodine		
Lysine	Iodine		
Maleic	Iodine		
Malic Acid	Iodine	epoxide	
Malic Acid	Iodine		
Malonic	Iodine		
Mandelic Acid	Iodine	epoxide	
Mandelic Acid	Iodine		
Methionine	Iodine		
Methionine	Iodine		
Methionine			
Nicotinamide			
Nicotinamide	Iodine	epoxide	peroxide
Nicotinic Acid	Iodine		
Nicotinic Acid			
Orotic acid	Iodine		
Orotic acid	Iodine	epoxide	peroxide
Oxalic acid	Iodine		
Palmitic acid	Iodine		
Pamoic acid	Iodine		
Pamoic acid			
Pamoic acid			

TABLE II

Co-crystal Former	Co-crystal Former Functional Group	Interacting Group						
Phenylalanine	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Phenylalanine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Piperazine	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Procaine	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Procaine	Ketone	alcohol		thiol	amide	amine	analine	phenol
Proline	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Proline	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
p-Toluenesulfonic acid	Sulfonic Acid	pyridine	ketone	aldehyde	ether	ester	amide	Carboxylic Acid
Pyridoxamine	Alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
Pyridoxamine	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Pyridoxamine	Pyridine	*alcohol		*	*amide	nitro	*amine	*Carboxylic Acid
Pyridoxine (4-Pyridoxic Acid)	Pyridine	*alcohol	pyridinium	*	*amide	nitro	*amine	*Carboxylic Acid
Pyridoxine (4-Pyridoxic Acid)	Alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
Pyroglutamic acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Pyroglutamic acid	Lactam	alcohol	ketone	thiol	amide	amine	analine	phenol
Quercetin	Ketone	alcohol		thiol	amide	amine	analine	phenol
Quercetin	Phenol	amine	amide	sulfoxide	n	pyridine	cyano	aldehyde
Quercetin	Ether	aromatic-N	amide	amine	aromatic_s	Sp2 amine	sulfoxide	chlorate
Resveratrol	Ketone	alcohol		thiol	amide	amine	analine	phenol
Resveratrol	Phenol	amine	amide	sulfoxide	n	pyridine	cyano	aldehyde
Saccharin	Amide	alcohol	ketone	thiol	amide	amine	analine	phenol
Saccharin	Ketone	alcohol		thiol	amide	amine	analine	phenol
Saccharin	Sulfoxide	pyridine	ketone	aldehyde	ether	ester	amide	Carboxylic Acid
Saccharin	Amine	alcohol	ketone	thiol	amide		analine	phenol
Salicylic Acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Salicylic Acid	Alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
Salicylic Acid, 4-amino	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Salicylic Acid, 4-amino	alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
Salicylic Acid, 4-amino	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol

TABLE II

Co-crystal Former									
Phenylalanine	phosphate	sulfate	sulfone	nitrate		pyridine		carboxilic acid	metals
Phenylalanine	phosphate	sulfate	sulfone	nitrate		pyridine		carboxilic acid	metals
Piperazine	phosphate	sulfate	sulfone	nitrate		pyridine		carboxilic acid	metals
Procaine	phosphate	sulfate	sulfone	nitrate		pyridine		carboxilic acid	metals
Procaine	phosphate	sulfate	sulfone	nitrate		pyridine		Carboxylic Acid	metals
Proline	phosphate	sulfate	sulfone	nitrate		pyridine		carboxilic acid	metals
Proline	phosphate	sulfate	sulfone	nitrate		pyridine		carboxilic acid	metals
p-Toluenesulfonic acid	amine	metals	thioether			sulfate	alcohol		
Pyridoxamine	phosphate	sulfate	sulfone	nitrate		pyridine		Carboxylic Acid	metals
Pyridoxamine	phosphate	sulfate	sulfone	nitrate		pyridine		carboxilic acid	metals
Pyridoxamine	*sulfonamide	*ketone	ether	triazole			ammonium	oxime	*chlorine
Pyridoxine									
(4-Pyridoxic Acid)	*sulfonamide	*ketone	ether	triazole			ammonium	oxime	*chlorine
Pyridoxine									
(4-Pyridoxic Acid)	phosphate	sulfate	sulfone	nitrate		pyridine		Carboxylic Acid	metals
Pyroglutamic acid	phosphate	sulfate	sulfone	nitrate		pyridine		carboxilic acid	metals
Pyroglutamic acid	phosphate	sulfate	sulfone	nitrate		pyridine		Carboxylic Acid	metals
Quercetin	phosphate	sulfate	sulfone	nitrate		pyridine		Carboxylic Acid	metals
Quercetin		alchohol		ester		ether	n-oxide	chlorine	fluorine
Quercetin	chlorine		cyano	ester		amine	nitro	nitrate	bromine
Resveratrol	phosphate	sulfate	sulfone	nitrate		pyridine		Carboxylic Acid	metals
Resveratrol		alchohol		ester		ether	n-oxide	chlorine	fluorine
Saccharin	phosphate	sulfate	sulfone	nitrate		pyridine		Carboxylic Acid	metals
Saccharin	phosphate	sulfate	sulfone	nitrate		pyridine		Carboxylic Acid	metals
Saccharin	amine	metals	thioether			sulfate	alcohol		
Saccharin	phosphate	sulfate	sulfone	nitrate		pyridine		Carboxylic Acid	metals
Salicylic Acid	phosphate	sulfate	sulfone	nitrate		pyridine		carboxilic acid	metals
Salicylic Acid	phosphate	sulfate	sulfone	nitrate		pyridine		Carboxylic Acid	metals
Salicylic Acid, 4-amino	phosphate	sulfate	sulfone	nitrate		pyridine		carboxilic acid	metals
Salicylic Acid, 4-amino	phosphate	sulfate	sulfone	nitrate		pyridine	carboxilic acid	metals	aldehyde
Salicylic Acid, 4-amino	phosphate	sulfate	sulfone	nitrate		pyridine		carboxilic acid	metals

TABLE II

Co-crystal Former								
Phenylalanine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Phenylalanine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Piperazine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Procaine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Procaine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Proline	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Proline	aldehyde	ester	ether	cyano		furan	bromine	chlorine
p-Toluenesulfonic acid								
Pyridoxamine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Pyridoxamine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
			n-heterocyclic					
Pyridoxamine		thiol	ring	thionedisulfide		iodine	hydrazone	thiocyanate
Pyridoxine			n-heterocyclic					
(4-Pyridoxic Acid)		thiol	ring	thionedisulfide	pyrrolidindione	iodine	hydrazone	thiocyanate
Pyridoxine								
(4-Pyridoxic Acid)	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Pyroglutamic acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Pyroglutamic acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Quercetin	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Quercetin	bromine	iodine	ketone	sulfonic acid	sulfate	phosphate	phosphonic acid	carboxylic acid
Quercetin	aldehyde	ketone	peroxide	epoxide			heterocyclic-S	iodine
Resveratrol	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Resveratrol	bromine	iodine	ketone	sulfonic acid	sulfate	phosphate	phosphonic acid	carboxylic acid
Saccharin	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Saccharin	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Saccharin	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Salicylic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Salicylic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Salicylic Acid, 4-amino	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Salicylic Acid, 4-amino	ester	ether	cyano		furan	bromine	chlorine	s-heterocyclic
Salicylic Acid, 4-amino	aldehyde	ester	ether	cyano		furan	bromine	chlorine

TABLE II

Co-crystal Former								
Phenylalanine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		
Phenylalanine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		
Piperazine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		
Procaine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		
Procaine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		
Proline	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		
Proline	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		
p-Toluenesulfonic acid								
Pyridoxamine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		
Pyridoxamine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		
Pyridoxamine	*bromine		hydroxamic acid	cyano	carboxamide	*sulfonic acid	*phosphoric acid	
Pyridoxine (4-Pyridoxic Acid)	*bromine		hydroxamic acid	cyano	carboxamide	*sulfonic acid	*phosphoric acid	
Pyridoxine (4-Pyridoxic Acid)	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		
Pyroglutamic acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		
Pyroglutamic acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		
Quercetin	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		
Quercetin	nitro	sulfone	analine					
Quercetin	ester	ether	carboxylic acid	sulfate	sulfone			alcohol
Resveratrol	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		
Resveratrol	nitro	sulfone	analine					
Saccharin	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		
Saccharin	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		
Saccharin	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		
Salicylic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		
Salicylic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		
Salicylic Acid, 4-amino	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		
Salicylic Acid, 4-amino	pyridine	cyano	n-heterocyclic	ketone	phosphate ester			fluorine
Salicylic Acid, 4-amino	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		

TABLE II

Co-crystal Former									
Phenylalanine	fluorine	carbamate	imidazole	BF4			N-SO2		thiourea
Phenylalanine	fluorine	carbamate	imidazole	BF4			N-SO2		thiourea
Piperazine	fluorine	carbamate	imidazole	BF4			N-SO2		thiourea
Procaine	fluorine	carbamate	imidazole	BF4			N-SO2		thiourea
Procaine	fluorine	carbamate	imidazole	BF4			N-SO2		thiourea
Proline	fluorine	carbamate	imidazole	BF4			N-SO2		thiourea
Proline	fluorine	carbamate	imidazole	BF4			N-SO2		thiourea
p-Toluenesulfonic acid									
Pyridoxamine	fluorine	carbamate	imidazole	BF4			N-SO2		thiourea
Pyridoxamine	fluorine	carbamate	imidazole	BF4			N-SO2		thiourea
Pyridoxamine	N-oxide	ester	ether	fluorine	acetate	thione	dithiadiazocyclopentadienyl		
Pyridoxine (4-Pyridoxic Acid)	N-oxide	ester	ether	fluorine	acetate	thione	dithiadiazocyclopentadienyl		
Pyridoxine (4-Pyridoxic Acid)	fluorine	carbamate	imidazole	BF4			N-SO2		thiourea
Pyroglutamic acid	fluorine	carbamate	imidazole	BF4			N-SO2		thiourea
Pyroglutamic acid	fluorine	carbamate	imidazole	BF4			N-SO2		thiourea
Quercetin	fluorine	carbamate	imidazole	BF4			N-SO2		thiourea
Quercetin									
Quercetin		phosphate	cyanamide						
Resveratrol	fluorine	carbamate	imidazole	BF4			N-SO2		thiourea
Resveratrol									
Saccharin	fluorine	carbamate	imidazole	BF4			N-SO2		thiourea
Saccharin	fluorine	carbamate	imidazole	BF4			N-SO2		thiourea
Saccharin	fluorine	carbamate	imidazole	BF4			N-SO2		thiourea
Salicylic Acid	fluorine	carbamate	imidazole	BF4			N-SO2		thiourea
Salicylic Acid	fluorine	carbamate	imidazole	BF4			N-SO2		thiourea
Salicylic Acid, 4-amino	fluorine	carbamate	imidazole	BF4			N-SO2		thiourea
Salicylic Acid, 4-amino	carbamate	imidazole	BF4						
Salicylic Acid, 4-amino	fluorine	carbamate	imidazole	BF4			N-SO2		thiourea

TABLE II

Co-crystal Former		
Phenylalanine	iodine	
Phenylalanine	iodine	
Piperazine	iodine	
Procaine	iodine	
Procaine	iodine	
Proline	iodine	
Proline	iodine	
p-Toluenesulfonic acid		
Pyridoxamine	iodine	epoxide
Pyridoxamine	iodine	
Pyridoxamine		
Pyridoxine		
(4-Pyridoxic Acid)		
Pyridoxine		
(4-Pyridoxic Acid)	iodine	epoxide
Pyroglutamic acid	iodine	
Pyroglutamic acid	iodine	epoxide peroxide
Quercetin	iodine	
Quercetin		
Quercetin		
Quercetin	iodine	
Resveratrol		
Resveratrol	iodine	
Saccharin	iodine	epoxide peroxide
Saccharin	iodine	
Saccharin		
Saccharin	iodine	
Salicylic Acid	iodine	
Salicylic Acid	iodine	epoxide
Salicylic Acid, 4-amino	iodine	
Salicylic Acid, 4-amino		
Salicylic Acid, 4-amino	iodine	

TABLE II

Co-crystal Former	Co-crystal Former Functional Group	Interacting Group						
Sebacic acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Serine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Serine	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Serine	Alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
Stearic acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Succinic Acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Tartaric Acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Threonine	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Threonine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Threonine	alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
Tris	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Tris	Alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
Tryptophan	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Tryptophan	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Tryptophan	Indole	*alcohol	pyridinium	*	*amide	nitro	*amine	*carboxilic acid
Tyrosine	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Tyrosine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Tyrosine	Alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
Urea	Ketone	alcohol		thiol	amide	amine	analine	phenol
Urea	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Urea	Amide	alcohol	ketone	thiol	amide	amine	analine	phenol
Valine	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Valine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Vitamin K5	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Vitamin K5	Alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
Xylitol	Alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol

TABLE II

Co-crystal Former								
Sebacic acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Serine	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Serine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Serine	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Stearic acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Succinic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Tartaric Acid	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Threonine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Threonine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Threonine	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Tris	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Tris	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Tryptophan	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Tryptophan	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Tryptophan	*sulfonamide	*ketone	ether	triazole		ammonium	oxime	*chlorine
Tyrosine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Tyrosine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Tyrosine	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Urea	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Urea	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Urea	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Valine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Valine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Vitamin K5	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Vitamin K5	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Xylitol	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals

TABLE II

Co-crystal Former								
Sebacic acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Serine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Serine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Serine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Stearic acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Succinic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Tartaric Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Threonine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Threonine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Threonine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Tris	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Tris	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Tryptophan	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Tryptophan	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Tryptophan		thiol	n-heterocyclic ring	thionedisulfide	pyrrolidindione	iodine	hydrazone	thiocyanate
Tyrosine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Tyrosine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Tyrosine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Urea	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Urea	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Urea	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Valine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Valine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Vitamin K5	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Vitamin K5	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Xylitol	aldehyde	ester	ether	cyano		furan	bromine	chlorine

TABLE II

Co-crystal Former							
Sebacic acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Serine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Serine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Serine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Stearic acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Succinic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Tartaric Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Threonine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Threonine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Threonine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Tris	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Tris	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Tryptophan	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Tryptophan	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Tryptophan	*bromine		hydroxamic acid	cyano	carboxamide	*sulfonic acid	*phosphoric acid
Tyrosine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Tyrosine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Tyrosine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Urea	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Urea	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Urea	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Valine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Valine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Vitamin K5	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Vitamin K5	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Xylitol	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	

TABLE II

Co-crystal Former								
Sebacic acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Serine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Serine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Serine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Stearic acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Succinic Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Tartaric Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Threonine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Threonine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Threonine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Tris	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Tris	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Tryptophan	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Tryptophan	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
	N-oxide	ester	ether	fluorine	acetate	thione	dithiadiazocyclopentadienyl	
Tryptophan	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Tyrosine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Tyrosine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Urea	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Urea	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Urea	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Valine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Valine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Vitamin K5	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Vitamin K5	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Xylitol	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea

TABLE II

Co-crystal Former			
Sebacic acid	iodine		
Serine	iodine		
Serine	iodine		
Serine	iodine	epoxide	
Stearic acid	iodine		
Succinic Acid	iodine		
Tartaric Acid	iodine		
Threonine	iodine		
Threonine	iodine		
Threonine	iodine	epoxide	
Tris	iodine		
Tris	iodine	epoxide	
Tryptophan	iodine		
Tryptophan	iodine		
Tryptophan			
Tyrosine	iodine		
Tyrosine	iodine		
Tyrosine	iodine	epoxide	
Urea	iodine		
Urea	iodine		
Urea	iodine	epoxide	peroxide
Valine	iodine		
Valine	iodine		
Vitamin K5	iodine		
Vitamin K5	iodine	epoxide	
Xylitol	iodine	epoxide	

TABLE III

Functional Group	Functional Group Structure	Interacting Group							
pyridine		*alcohol	pyridinium	*amide	nitro	*amine	*carboxilic acid
imidazole		imidazole	chlorine	acetamide	carboxylate	thione	nitro
Hydroxamic acid		hydroxamic acid	alcohol	phosphinic ester	alkane	pyridine	amide
peroxide		ester	peroxide	amide	ether	alkane	N-heterocycle
epoxide		alkane	bromine	alcohol	ester	epoxide	amide
thioester		aromatic	thioester	alkane	sulfamide	hydroxy	bromine

TABLE III

Functional Group												
pyridine	*sulfonamide	*ketone	ether	triazole	alkane	ammonium	oxime	*chlorine	alkyne			
imidazole	cyanamide	ketone	cyano	carboxilic acid	alcohol	alkane	thiol	amine	phosphinic acid hemihydrate			
Hydroxamic acid	sulfonamide	carboxylate	phosphine	amine	aromatic							
peroxide	aromatic	alcohol	pyrimidinedione	analine	thiazole	peroxy acid	ketone	carboxilic acid	azide			
epoxide	alkene	hydrazone	aromatic	thioether	ketone	aldehyde	chlorine	carboxilic acid	alkyne			
thioester	iodine	amine	cyano	thioketone	amide		chlorine	nitro				

TABLE III

Functional Group										
pyridine	thiol	n-heterocyclic ring	thionedisulfide	pyrrolidindione	iodine	hydrazone	thiocyanate	bromine	aromatic
imidazole	chlorine	sulfonyl	sulfoxide	amide	fluorine	sulfonate ester			
Hydroxamic acid									
peroxide	phosphine oxide	sulfonamide	aniline						
epoxide		ammonium	fluorine	nitro	amine	cyano			
thioester									

TABLE III

Functional Group													
	hydroxamic acid	cyano	carboxamide	*sulfonic acid	*phosphoric acid	N-oxide	ester	ether	fluorine	acetate	thione
pyridine											
imidazole											
Hydroxamic acid											
peroxide											
epoxide											
thioester											

TABLE III

Functional Group							
pyridine	dithiadiazocyclopentadienyl						
imidazole							
Hydroxamic acid							
peroxide							
epoxide							
thioester							

TABLE III

Functional Group	Functional Group Structure	Interacting Group						
thioketone		alkane	thioketone	ketone	SULFAMIDE	AMINE	thiol	
nitrate ester		aromatic	amide	alkane	chlorine	nitrate ester	bromine	
Thiophosphate ester-O		amine	imidazole	cyclic amide				
Phosphate ester		aromatic	alcohol	phosphate ester	aromatic N-ring	pyridine	aniline	
Ketone		alcohol	ketone	thiol	amide	amine	aniline	
Aldehyde		alcohol	ketone	thiol	amide	amine	aniline	
Thiol		carboxylic acid	sodium	aldehyde	ketone	aromatic-N	cadmium	

TABLE III

Functional Group												
thioketone	sulfoxide	oxo	chlorine	bromine	AROMATIC	alkene	sulfone	iodine	AZOXY			
nitrate ester	alcohol	ether	acetate									
Thiophosphate ester-O												
Phosphate ester	amine		sodium	potassium	lithium	carboxylic acid	amide	alkane				
Ketone	phenol	phosphate	sulfate	sulfone	nitrate	pyridine	aromatic	carboxilic acid	metals			
Aldehyde	phenol	phosphate	sulfate	sulfone	nitrate	pyridine	aromatic	carboxilic acid	metals			
Thiol	alkane	arsenic	chlorine	alcohol	potassium	Ru	aromatic	Rb	Sb			

TABLE III

Functional Group										
thioketone	potassium	epoxide	n-oxide	cyano	iron	cobalt	amine	sulfate		
nitrate ester										
Thiophosphate ester-O										
Phosphate ester										
Ketone	aldehyde	ester	ether	cyano		furan	bromine	chlorine	s-heterocyclic	
Aldehyde	aldehyde	ester	ether	cyano		furan	bromine	chlorine	s-heterocyclic	
Thiol										

TABLE III

Functional Group														
thioketone														
nitrate ester														
Thiophosphate ester-O														
Phosphate ester														
Ketone	pyridine	cyano	n-heterocyclic	ketone	phosphate ester			fluorine	carbamate	imidazole	BF4	alkane		
Aldehyde	pyridine	cyano	n-heterocyclic	ketone	phosphate ester			fluorine	carbamate	imidazole	BF4	alkane		
Thiol														

TABLE III

Functional Group								
thioketone								
nitrate ester								
Thiophosphate ester-O								
Phosphate ester								
Ketone	aromatic	N-SO2	thiourea	iodine				
Aldehyde	aromatic	N-SO2	thiourea	iodine	epoxide			
Thiol								

TABLE III

Functional Group	Functional Group Structure	Interacting Group							
Alcohol		alcohol	ketone	thiol	amide	amine	analine		
Thioether		aromatic-N	amide	amine	aromatic_s	Sp2 amine	sulfoxide		
Ether		aromatic-N	amide	amine	aromatic_s	Sp2 amine	sulfoxide		
Cyanamide		cyano	amine	potassium	aromatic-N	bromine	sodium		
Thiocyanate		aromatic-S	ester	ether					
sP2 amine		thioether	ether	metals	MoOCl4	BF4	bromine		
Amine primary		alcohol	ketone	thiol	amide	amine	analine		

TABLE III

Functional Group											
Alcohol	phenol	phosphate	sulfate	sulfone	nitrate	pyridine	aromatic	carboxilic acid	metals		
Thioether	chlorate	chlorine	alkyne	cyano	ester	amine	nitro	nitrate	bromine		
Ether	chlorate	chlorine	alkyne	cyano	ester	amine	nitro	nitrate	bromine		
Cyanamide	imidazole	ether	n-heterocyclic	alcohol	cesium	Ag					
Thiocyanate											
sP2 amine	chlorine		Sp2 amine	sulfate	Osmium						
Amine primary	phenol	phosphate	sulfate	sulfone	nitrate	pyridine	aromatic	carboxilic acid	metals		

TABLE III

Functional Group											
Alcohol	aldehyde	ester	ether	cyano		furan	bromine		chlorine	s-heterocyclic
Thioether	aldehyde	ketone	peroxide	epoxide	Ag	Se	heterocyclic-S	iodine	ester	
Ether	aldehyde	ketone	peroxide	epoxide	Ag	Se	heterocyclic-S	iodine	ester	
Cyanamide										
Thiocyanate										
sP2 amine										
Amine primary	aldehyde	ester	ether	cyano		furan	bromine	chlorine	s-heterocyclic	

TABLE III

Functional Group														
Alcohol	pyridine	cyano	n-heterocyclic	ketone	phosphate ester			fluorine	carbamate	imidazole	BF4			
Thioether	ether	carboxylic acid	sulfate	sulfone	alkane	alcohol			phosphate					
Ether	ether	carboxylic acid	sulfate	sulfone	alkane	alcohol			phosphate	cyanamide				
Cyanamide														
Thiocyanate														
sP2 amine														
Amine primary	pyridine	cyano	n-heterocyclic	ketone	phosphate ester			fluorine	carbamate	imidazole	BF4			
												alkane		

TABLE III

Functional Group							
Alcohol	aromatic	N-SO2	thiourea	iodine	epoxide		
Thioether							
Ether							
Cyanamide							
Thiocyanate							
sP2 amine							
Amine primary	aromatic	N-SO2	thiourea	iodine			

TABLE III

Functional Group	Functional Group Structure	Interacting Group						
Amine secondary		alcohol	ketone	thiol	amide	amine	amine	analine
Amine tertiary		alcohol	ketone	thiol	amide	amine	amine	analine
Amide		alcohol	ketone	thiol	amide	amine	amine	analine
Sulfonic acid		pyridine	ketone	aldehyde	ether	ester	amide	
Phosphinic acid		alkane	potassium	lithium	n-heterocyclic	oxime	amide	
Phosphonic acid		alkane	potassium	lithium	n-heterocyclic	oxime	amide	
Carboxylic acid		alcohol	ketone	thiol	amide	amine	amine	analine

TABLE III

Functional Group											
Amine secondary	phenol	phosphate	sulfate	sulfone	nitrate	pyridine	aromatic	carboxilic acid	metals		
Amine tertiary	phenol	phosphate	sulfate	sulfone	nitrate	pyridine	aromatic	carboxilic acid	metals		
Amide	phenol	phosphate	sulfate	sulfone	nitrate	pyridine	aromatic	carboxilic acid	metals		
Sulfonic acid	carboxilic acid	amine	metals	thioether		sulfate	alcohol				
Phosphinic acid	phenol	aromatic	amine	alcohol		metals					
Phosphonic acid	phenol	aromatic	amine	alcohol		metals	carboxylic acid	Sp2 amine	aniline		
Carboxylic acid	phenol	phosphate	sulfate	sulfone	nitrate	pyridine	aromatic	carboxilic acid	metals		

TABLE III

Functional Group											
Amine secondary	aldehyde	ester	ether	cyano		furan	bromine	chlorine	s-heterocyclic		
Amine tertiary	aldehyde	ester	ether	cyano		furan	bromine	chlorine	s-heterocyclic		
Amide	aldehyde	ester	ether	cyano		furan	bromine	chlorine	s-heterocyclic		
Sulfonic acid											
Phosphinic acid											
Phosphonic acid	ether	phosphonic acid	aromatic-N	ketone	aldehyde	imidazole					
Carboxylic acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine	s-heterocyclic		

TABLE III

Functional Group												
Amine secondary	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	fluorine	carbamate	imidazole	BF4	alkane		
Amine tertiary	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	fluorine	carbamate	imidazole	BF4	alkane		
Amide	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	fluorine	carbamate	imidazole	BF4	alkane		
Sulfonic acid												
Phosphinic acid												
Phosphonic acid												
Carboxylic acid	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	fluorine	carbamate	imidazole	BF4	alkane		

TABLE III

Functional Group							
Amine secondary	aromatic	N-SO2	thiourea	iodine			
Amine tertiary	aromatic	N-SO2	thiourea	iodine			
Amide	aromatic	N-SO2	thiourea	iodine	epoxide	peroxide	
Sulfonic acid							
Phosphinic acid							
Phosphonic acid							
Carboxylic acid	aromatic	N-SO2	thiourea	iodine			

TABLE III

Functional Group	Functional Group Structure	Interacting Group						
Sulfate ester		pyridine	ketone	aldehyde	ether	ester	amide	
Oxime		alcohol	alkane	amine	amide	ether	ester	
Nitrile		metal	ketone	phenol	alcohol		cyano	
Diazo		Oxime						
Nitro		pyridine	ketone	aldehyde	ether	ester	amide	
S-heterocyclic ring		alcohol	thioketone	thioether	s-heterocyclic	ketone	aromatic	
Thiophene		chlorine	fluorine	amide	ketone	NO	SO	

TABLE III

Functional Group											
Sulfate ester	carboxilic acid	amine	metals	thioether	sulfate	alcohol					
Oxime	pyridine	n-aromatic	chlorate	chlorine	Sp2-N	diazo	thioketone	cyano	n-oxide		
Nitrile	amine	analine	bromine	amide	alkane	carboxylic acid	chlorine	n-heterocyclic	aromatic		
Diazo											
Nitro	carboxilic acid	amine	metals	thioether	sulfate	alcohol					
S-heterocyclic ring	alkene	amine	chlorine	BF4	sulfate	ester	NO	ether	amide		
Thiophene	CO										

TABLE III

Functional Group													
Sulfate ester													
Oxime	ketone	aldehyde	carboxylic acid	bromine	aromatic	pyridine	BF4						
Nitrile	potassium	aldehyde	thioether	pyridine	n-aromatic	bromine	ether	s-aromatic	thiophene				
Diazo													
Nitro													
S-heterocyclic ring	iodine	carboxylic acid	sodium	cyano	chloride	furan							
Thiophene													

TABLE III

Functional Group												
Sulfate ester												
Oxime												
Nitrile												
Diazo												
Nitro												
S-heterocyclic ring												
Thiophene												

TABLE III

Functional Group						
Sulfate ester						
Oxime						
Nitrile						
Diazo						
Nitro						
S-heterocyclic ring						
Thiophene						

TABLE III

Functional Group	Functional Group Structure	Interacting Group					
N-heterocyclic ring		alcohol	thioketone	thioether	s-heterocyclic	ketone	aromatic
O-heterocyclic ring		alcohol	thioketone	thioether	s-heterocyclic	ketone	aromatic
Pyrrole		chlorine	fluorine	amide	ketone	NO	SO
Furan		s-heterocyclic					

TABLE III

Functional Group											
N-heterocyclic ring	alkene	amine	chlorine	BF4	sulfate	ester	NO	ether	amide		
O-heterocyclic ring	alkene	amine	chlorine	BF4	sulfate	ester	NO	ether	amide		
Pyrrole	CO	imidazole	pyridine	n-aromatic	aldehyde	carboxylic acid	sulfate	chlorine	bromine		
Furan											

TABLE III

Functional Group										
N-heterocyclic ring	iodine	carboxylic acid	sodium	cyano	chloride	aldehyde				
O-heterocyclic ring	iodine	carboxylic acid	sodium	cyano	chloride	aldehyde				
Pyrrole	oxime	alcohol	phenol	ester	ether					
Furan										

TABLE III

Functional Group												
N-heterocyclic ring												
O-heterocyclic ring												
Pyrrole												
Furan												

TABLE III

Functional Group						
N-heterocyclic ring						
O-heterocyclic ring						
Pyrrole						
Furan						

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
(-)-amlodipine	3,5-Pyridinedicarboxylic acid, 2-((2-aminoethoxy)methyl)-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl-5-methyl ester, (S)- [CAS]	103129-82-4	WO	9310779	Antihypertensive, other	Hypertension, general
(-)-halofenate	(-)-Benzeneacetic acid, 4-chloro-Alpha-[3-(trifluoromethyl)-phenoxy]-, 2-(acetylamino)ethyl ester		US	6262118	Antidiabetic	Diabetes, Type II
(R)-salbutamol	1,3-Benzenedimethanol, Alpha1-(((1,1-dimithylethyl)amino)methyl)-4-hydroxy- [CAS]				Formulation, modified-release, <=24hr	Asthma
(R)-salbutamol	1,3-Benzenedimethanol, Alpha1-(((1,1-dimethylethyl)amino)methyl)-4-hydroxy- [CAS]	34391-04-3	US	5547994	Antiasthma	Asthma
(R,R)-formoterol	Formamide, N-(2-hydroxy-5-((1-hydroxy-2-((2-(4-methoxyphenyl)-1-methylethyl)amino)ethyl)phenyl)- (R-(R*,R*))- [CAS]	67346-49-0	US	5795564	Antiasthma	Asthma
(S)-doxazosin	(S)-1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(1,4-benzodioxan-2-yl carbonyl)piperazine	70918-18-2	WO	9409785	Prostate disorders	Benign prostatic hyperplasia
(S)-fluoxetine	Benzenepropanamide, N-methyl-Gamma-(4-(trifluoromethyl)phenoxy)- (S)				Antimigraine	Migraine
(S)-oxybutynin	Benzeneacetic acid, Alpha-cyclohexyl-Alpha-hydroxy-, 4-(diethylamino)-2-butynyl ester, (S)- [CAS]	119618-22-3			Urological	Incontinence
1,2-Naphthoquinone		524-42-5				
17α-Hydroxyprogesterone		68-96-2				
17-Methyltestosterone		58-18-4				
195mPt-cisplatin	Platinum-195m, diamminedichloro, (SP-4-2)-		US	6074626	Anticancer, alkylating	Cancer, liver
1α-Hydroxycholecalciferol		41294-56-8				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference	Example of Therapeutic Use	Example of Indication
1-Naphthyl Salicylate		550-97-0			
1-Naphthylamine-4-sulfonic Acid		84-86-6			
1-Theobromineacetic Acid		5614-56-2			
2,4,6-Tribromo-m-cresol		4619-74-3			
2,6-Diamino-2'-butyloxy-3,5'-azopyridine		617-19-6			
21-Acetoxypregnenolone		566-78-9			
2-Amino-4-picoline		695-34-1			
2-Aminothiazole		96-50-4			
2-ethoxybenzoic acid	2-Ethoxybenzoic acid		IDE 5134001	Analgesic, NSAID	Pain, general
2-Naphthol		135-19-3			
2-Naphthyl Benzoate		93-44-7			
2-Naphthyl Lactate		93-43-6			
2-Naphthyl Salicylate		613-78-5			
2-P-Sulfanilylanilinoethanol		80-02-4			
2-Thiouracil		141-90-2			
3',3'',5',5''-Tetrabromophenolphthalein		76-62-0			
3-Amino-4-hydroxybutyric Acid		589-44-6			
3-Bromo-d-camphor		76-29-9			
3-Hydroxycamphor		10373-81-6			
3-O-Lauroylpyridinol		1562-13-6			
Diacetate					
3-Pentadecylcatechol		492-89-7			

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference	Example of Therapeutic Use	Example of Indication
3-Quinuclidinol		1619-34-7			
4,4'-Oxydi-2-butanol		821-33-0			
4,4'-Sulfinyldianiline		119-59-5			
4-Amino-3-hydroxybutyric acid		352-21-6			
4-Amino-3-phenylbutyric Acid		1078-21-3			
4-aminosalicylic acid	Benzoic acid, 4-amino-2-hydroxy- [CAS]	65-49-6		GI inflammatory/bowel disorders	Inflammatory bowel disease
4-Chloro-m-cresol		59-50-7			
4-Hexylresorcinol		136-77-6			
4-Salicyloylmorpholine		3202-84-4			
5'-Nitro-2'-propoxyacetanilide		553-20-8			
5-aminolevulinic acid,	Pentanoic acid, 5-amino-4-oxo- [CAS]	106-60-5		Dermatological	Keratosis
5-azacitidine	1,3,5-Triazin-2(1H)-one, 4-amino-1-ß-D-ribofuranosyl- [CAS]	320-67-2		Anticancer, antimetabolite	Myelodysplastic syndrome
5-Bromosalicylhydroxamic Acid		5798-94-7			
5F-DF-203	2-(4-Amino-3-methylphenyl)-6-hydroxybenzothiazole			Anticancer, other	Cancer, breast
5-FU	2,4(1H,3H)-Pyrimidinedione, 5-fluoro [CAS]	51-21-8		Formulation, parenteral, targeted	Cancer, general
5-HT3 antagonists			US 6037360	Male sexual dysfunction	Premature ejaculation
6-Azauridine		54-25-1			
6-Mercaptopurine		50-44-2			
8-Hydroxyquinoline		148-24-3			
9-Aminocamptothecin		91421-43-1			
A-151892	N-[2-[2,2,2-Trifluoro-1-hydroxy-1-(trifluoromethyl)-ethyl]-naphthalen-1-yl] amide			Urological	Overactive bladder

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
α1-Antitrypsin		9041-92-3				
A-5021	6H-Purin-6-one, 2-amino-9-[(1S,2R)-1,2-bis(hydroxymethyl)cyclopropyl]methyl-1,9-dihydro- [CAS]	145512-65-2			Antiviral, other	Infection, varicella zoster virus
abacavir	2-Cyclopentene-1-methanol, 4-(2-amino-6-(cyclopropylamino)-9H-purin-9-yl)-, (1S-cis)- [CAS]	136470-78-5	EP	434450	Antiviral, anti-HIV	Infection, HIV/AIDS
altaperidone	7,3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]propoxy]-3-(hydroxymethyl)chromen-4-one	183849-43-6	WO	9632389	Neuroleptic	Schizophrenia
atarelix	D-Alaninamide, N-acetyl-3-(2-naphthalenyl)-D-alanyl-4-chloro-D-phenylalanyl-3-(3-pyridinyl)-D-alanyl-L-seryl-N-methyl-L-tyrosyl-D-asparaginyl-L-leucyl-N6-(1-methylethyl)-L-lysyl-L-prolyl- [CAS]	183552-38-7	US	5843902	Anticancer, hormonal	Cancer, prostate
Abcximab		1436653-53-6				
Abecarnil		1111841-85-1				
abetimus	Androsta-5,16-dien-3-ol, 17-(3-pyridinyl)-, acetate (ester), (3β)- [CAS]	169147-32-4	US	5552391	Immunosuppressant	Lupus erythematosus, systemic
abiraterone		154229-18-2	GB	2265624	Anticancer, hormonal	Cancer, prostate
α-Bisabolol		515-69-5				
ABLC	Amphotericin B [CAS]	1397-89-3			Formulation, conjugate, carbohydrate	Infection, Candida, general
ABT-751	Benzenesulfonamide, N-[2-[(4-hydroxyphenyl)amino]-3-pyridinyl]-4-methoxy- [CAS]	300552-87-0				
AC-5216	N-benzyl-N-ethyl-2-(7,8-dihydro-7-methyl-8-oxo-2-phenyl-9H-purin-9-yl)acetamide	141430-65-1	EP	472053	Anticancer, other	Cancer, general
Acadesine		2627-69-2			Anxiolytic	Anxiety, general
acamprosate	1-Propanesulfonic acid, 3-(acetylamino)- [CAS]	77337-76-9	GB	2051789	Dependence treatment	Addiction, alcohol
Acamprosate		77337-73-6				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Acarbose		56180-94-0				
acebrophylline	7H-Purine-7-acetic acid, 1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo-, compd. with trans-4-[[(2-amino-3,5-dibromophenyl)methyl]amino]cyclohexanol (1:1) [CAS]	96689-76-3	DE	3425007	Antiasthma	Asthma
acebutolol	Butanamide, N-[3-acetyl-4-[2-hydroxy-3-[(1-methylethyl)amino]propoxy]phenyl]-, (+/-)- [CAS]	34381-68-5 37517-30-9	US	3726919	Antihypertensive, adrenergic	
Acecainide		32795-44-1				
Acecarbromal		77-66-7				
aceclofenac	Benzeneacetic acid, 2-[(2,6-dichlorophenyl)amino]-, carboxymethyl ester [CAS]	89796-99-6	EP	119832	Anti-inflammatory	Pain, musculoskeletal
Acedapsone		77-46-3				
Acediasulfone		80-03-5				
Acefylline		652-37-9				
Aceglutamide		2490-97-3				
aceglutamide	Aluminum, pentakis(N2-acetyl-L-glutaminato)tetrahydroxytri- [CAS]	12607-92-0	DE	2127176	Antiulcer	Ulcer, GI, general
acemetacin	1H-Indole-3-acetic acid, 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-, carboxymethyl ester [CAS]	53164-05-9	US	3910952	Anti-inflammatory	
Acenocoumarol		152-72-7				
Acetal		105-57-7				
Acetamidosuccinol		305-13-5				
Acetaminophen		103-90-2				
Acetaminosalol		118-57-0				
Acetanilide		103-84-4				
Acetarsone		97-44-9				
Acetazolamide		59-66-5				
Acetiamine		299-89-8				
Acetohexamide		968-81-0				
Acetohydroxamic Acid		546-88-3				
Acetophenazine		2751-68-0				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Acetophenone		98-86-2				
Acetosulfone		128-12-1				
acetoxolone	Olean-12-en-30-oic acid, 3b-hydroxy-11-oxo-,acetate, aluminium salt [CAS]	29728-34-5 6277-14-1	US	3764618	Antiulcer	
Acetrizoate		129-63-5				
Acetyl Sulfamethoxypyrazine		3590-05-4				
Acetylcamitine		14992-62-2				
Acetylcholine		66-23-9				
Acetylcholine		60-31-1				
Acetylcysteine		616-91-1				
Acetyleucine		149-90-6				
Monoethanolamine						
Acetylpheneturide		13402-08-9				
acetylsalicylic acid	Benzoic acid, 2-(acetyloxy)- [CAS]	50-78-2 75-6	530		Formulation, optimized, microencapsulate	Pain, general
α-Chloralose		15879-93-3				
aciclovir	6H-Purin-6-one, 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]- [CAS]	59277-89-3			Formulation, dermal, topical	Infection, herpes simplex virus
Acifran		72420-38-3				
acipimox	Pyrazinecarboxylic acid, 5-methyl-, 4-oxide [CAS]	51037-30-0	GB	1391967	Hypolipaemic/Antiatherosclerosis	Hyperlipidaemia, general
aclarubicin	Acetic acid, oxo[[3-(1H-tetrazol-5-yl)phenyl]amino]- [CAS]	114607-46-4	EP	256507	Ophthalmological	Conjunctivitis
acitretin	2,4,6,8-Nonatetraenoic acid, 9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-, (all-E)- [CAS]	55079-83-9 57576-44-0	GB	1459401	Antipsoriasis	Psoriasis
aclarubicin		75443-99-1	US	3988315	Anticancer, antibiotic	
Aclatonium Napadisilate		550077-30-0				
Aconitine		302-27-2				
Acranil®		1684-42-0				
Acriflavine		8048-52-0				
Acrisorcin		7527-91-5				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
acrivastine	2-Propenoic acid, 3-[6-[1-(4-methylphenyl)-3-(1-pyrrolidinyl)-1-propenyl]-2-pyridinyl]-, (E,E)- [CAS]	87848-99-5	EP	869659	Antipruritic/inflamm, allergic	Rhinitis, allergic, general
acrivastine + pseudoephedrine	Benzenemethanol, Alpha-[1-(methylamino)ethyl]-, hydrochloride, [S-(R*,R*)]-, mixt.with 2-Propenoic acid, 3-[6-[1-(4-methylphenyl)-3-(1-pyrrolidinyl)-1-propenyl]-2-pyridinyl]-, (E,E)-				Antiallergic, non-asthma	Rhinitis, allergic, seasonal
adagardine derivative	3,3-dimethyl-1-propylamide HCl monoacetonamide adagardine				Peptide antibiotic	Infection, general
Actarit		18699-02-0				
ACTH		9002-60-2				
Acyclovir		59277-89-3				
adapalene	2-Naphthalenecarboxylic acid, 6-(4-methoxy-3-tricyclo[3.3.1.13,7]dec-1-ylphenyl)- [CAS]	106685-40-9	EP	199836	Antiacne	Acne
ADCON-L	GL 402 [CAS]	137802-74-5			Formulation, other	Fibrosis, epidural
Adefovir		106941-25-7				
adefovir dipivoxil	Propanoic acid, 2,2-dimethyl-, ((((2-(6-amino-9H-purin-9-yl)ethoxy)methyl)phosphinylidene)bis(oxymethylene)ester- [CAS]	142340-99-6	EP	205826	Antiviral, other	Infection, hepatitis B virus
Adenoscan	6-Amino-9-ß-D-ribofuranosyl-9H-purine [CAS]	58-61-7			Imaging agent	Diagnosis, coronary
Adenosine Triphosphate		56-65-5				
ADEPT		159079-88-8			Immunoconjugate, other	Cancer, colorectal
Adinazolam		37115-32-5				
Adiphenine		64-95-9				
ADL-10-0101			WO	9732857	Analgesic, other	Pain, general
Adrafinil		63547-13-7				
Adrenalone		99-45-6				
Adrenochrome		54-06-8				
adrogolide	Benzo(f)thiinno(2,3-c)quinoline-9,10-diol, 4,5,5a,6,7,11b-hexahydro-2-propyl-, diacetate (ester), hydrochloride (5aR-trans)- [CAS]	166591-11-3 171752-56-0	US	5597832	Dependence treatment	Addiction, cocaine

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
AEOL-10150	,		US	6103714	Neuroprotective	Unspecified
AET		56-10-0				
α-Ethylbenzyl Alcohol		93-54-9				
AF-2259	Benzeneacetic acid, Alpha-methyl-4-(2-methylpropyl)-, 2-methoxyphenyl ester [CAS]	66332-77-2	DE	2726435	Anti-inflammatory	Inflammation, general
Afloqualone		56287-74-2				
AG-041R	1H-Indole-3-acetamide, 1-[2,2-diethoxyethyl)-2,3-dihydro-N-(4-methylphenyl)-3-(((4-methylphenyl)amino)carbonyl)amino)-2-oxo-, (3R)- [CAS]	199800-49-2	WO	9419322	Alimentary/Metabolic, other	Unspecified
AG-2037	N-(5-[2-(2-amino-4(3H)-oxo-5,6,7,8-tetrahydropyrido[2,3-d]pyrimidin-6-yl)ethyl]-4-methylthieno-2-yl)glutamic acid				Anticancer, antimetabolite	Cancer, general
α-Glucose-1-phosphate		59-56-3				
AGN-194310	Benzoic acid, 4-[(5,6-dihydro-5,5,8,8-tetramethyl-2-(4-ethylphenyl)-2H-1-benzothiopyran-6-yl)ethynyl]- [CAS]	229961-45-9	WO	9709297	Dermatological	Psoriasis
agomelatine	Acetamide, N-[2-(7-methoxy-1-naphthalenyl)ethyl]- [CAS]	138112-76-2	EP	447285	Antidepressant	Sleep disorder, general
Ahistan		518-61-6				
AHL-157			US	5411972	Hypolipaemic/Antiatherosclerosis	Atherosclerosis
AIT-034	9H-Purine-6-propanamide, 1,6-dihydro-6-oxo-N-[3-(2-oxo-1-pyrrolidinyl)propyl]- [CAS]	138117-48-3	US	5447939	Cognition enhancer	Dementia, senile, general
AIT-202	N-[2-(5-Hydroxy-1H-indol-3-yl)ethyl]-3-(6-oxo-6,9-dihydro-1H-purin-9-yl)propionamide		WO	9957120	Antidepressant	Unspecified

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
AJ-9677	Acetic acid, ((3-((2R)-2-((2R)-2-(3-chlorophenyl)-2-hydroxy-ethyl)amino)propyl)-1H-indol-7-yl)oxy)- [CAS]	244081-42-3			Antidiabetic	Diabetes, Type II
AJG-949			WO	9733885	Gastroprokinetic	Motility dysfunction, GI, general
Ajmaline		12/07/4360				
Alacepril		74258-86-9				
albaconazole	4(3H)-Quinazolinone, 7-chloro-3-[(1R,2R)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]- [CAS]	187949-02-6	WO	9705131	Antifungal	Infection, Candida, general
albendazole	Carbamic acid, [5-(propylthio)-1H-benzimidazol-2-yl]-, methyl ester [CAS]	54029-12-8 54965-21-8 18559-94-9	GB	1464326	Anthelmintic	Infection, helminth, general
Albuterol		830-89-7				
Alfutoin						
alclofenac	Benzeneacetic acid, 3-chloro-4-(2-propenyloxy)- [CAS]	22131-79-9	GB	1174535	Anti-Inflammatory	
aldometasone	Pregna-1,4-diene-3,20-dione, 7-chloro-11-hydroxy-16-methyl-17,21-bis(2-oxopropoxy)-, (7Alpha,11Β,16Alpha)- [CAS]	86734-13-2 67452-97-5	US	4124707	Antipruritic/antiamn, allergic	Inflammation, dermal
Alcuronium		23214-96-2				
Aldioxa		5579-81-7				
Aldol		107-89-1				
Aldosterone		52-39-1				
alendronate	Phosphonic acid, (4-amino-1-hydroxybutylidene)bis-[CAS]	121268-17-5 129318-43-0	GB	2119042	Osteoporosis treatment	Osteoporosis
Alendronic Acid		66376-36-1				
Alexidine		22573-93-9				
alfacalcidol	9, 10-Secocholesta-5,7,10(19)-triene-1,3-diol, (1Alpha,3Β,5Z,7E)- [CAS]	41294-56-8			Osteoporosis treatment	Osteodystrophy
Alfadolone		23930-37-2				
Alfaxalone		23930-19-0				
Alfentanil		71195-58-9				
alfimeprase		259074-76-5			Fibrinolytic	Peripheral vascular disease

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
alfuzosin	2-Furancarboxamide, N-[3-[(4-amino-6,7-dimethoxy-2-quinazolinyl)methylamino]propyl]tetrahydr o- [CAS]	81403-68-1 81403-80-7	GB	2013679	Prostate disorders	Benign prostatic hyperplasia
alfuzosin	2-Furancarboxamide, N-[3-[(4-amino-6,7-dimethoxy-2-quinazolinyl)methylamino]propyl]tetrahydr o- [CAS]	81403-68-1 81403-80-7			Formulation, modified-release, other	Benign prostatic hyperplasia
Algestone		595-77-7				
Algestone Acetophenide		24356-04-3				
Algin		9005-38-3				
Alglucerase		1430103-46-7				
Alibendol		26750-81-2				
aliskiren	(2S,4S,5S,7S)-5-Amino-N-(2-carbamoyl-2-methylpropyl)-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methylnonanamide	1733334-57-1			Antihypertensive, renin system	Hypertension, general
alitretinoin	9-cis retinoic acid	03/09/5300			Antipruritic/inflamm, allergic	Eczema, general
alizapride	1H-Benzotriazole-5-carboxamide, 6-methoxy-N-[[1-(2-propenyl)-2-pyrrolidinyl]methyl]- [CAS]	59338-93-1	GB	1475234	Antiemetic	Nausea and vomiting, general
Alkannin		517-88-4				
Alkofanone		7527-94-8				
Allantoin		97-59-6				
Allobarbital		52-43-7				
Allopurinol		315-30-0				
Allyl Isothiocyanate		57-06-7				
Allylestrenol		432-60-0				
almagate	Magnesium, [carbonato(2-)]heptahydroxy(aluminum)di-, dihydrate [CAS]	66827-12-1 72526-11-5	US	4447417	Antacid/Antiflatulent	
alminoprofen	Benzeneacetic acid, Alpha-methyl-4-[(2-methyl-2-propenyl)amino]- [CAS]	39718-89-3	US	3957850	Analgesic, NSAID	

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
almitrine	1,3,5-Triazine-2,4-diamine, 6-[4-[bis(4-fluorophenyl)methyl]-1-piperazinyl]-N,N'-di-2-propenyl-, dimethanesulfonate [CAS]	27469-53-0 29608-49-9	GB	1256513	Respiratory	Bronchitis, chronic
almotriptan	Pyrrolidine, 1-(((3-(2-(dimethylamino)ethyl)-1H-indol-5-yl)methyl)sulfonyl)- [CAS]	154323-57-6	WO	9402460	Antimigraine	Migraine
Aloe-Emodin		481-72-1				
Aloin		5133-19-7				
alosetron	2,3,4,5-Tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one [CAS]	122852-42-0 122852-69-1 132414-02-9	EP	306323	GI inflammatory/bowel disorders	Irritable bowel syndrome
alovudine	Thymidine, 3'-deoxy-3'-fluoro- [CAS]	25526-93-6	EP	470355	Antiviral, anti-HIV	Infection, HIV/AIDS
Aloxiprin		9014-67-9				
Alpha-1 protease inhibitor			US	5780014	Formulation, inhalable, topical	Emphysema, alpha-1 antitrypsin deficiency
Alpha-dihydroergocryptine	Ergocryptine, 9,10-dihydro-, methanesulfonate (salt)- [CAS]	29261-93-6			Formulation, other	Parkinson's disease
Alphaprodine		77-20-3				
Alpidem		82626-01-5				
Alpiropride		81982-32-3				
alprazolam	4H-[1,2,4]Triazolo[4,3-a][1,4]benzodiazepine, 8-chloro-1-methyl-6-phenyl-[CAS]	28981-97-7	US	3987052	Anxiolytic	Anxiety, general
Alprenolol		13655-52-2				
alsactide	Alpha1-17-Corticotropin, 1-ß-alanine-17-[N-(4-aminobutyl)-L-lysinamide]- [CAS]	34765-96-3	US	3749704	ACTH	Arthritis, rheumatoid
ALT-711	Thiazolium, 4,5-dimethyl-3-(2-oxo-2-phenylethyl)-, bromide [CAS]	181069-80-7	WO	9622095	Symptomatic antidiabetic	Hypertension, general
Althiazide		5588-16-9				
altinicline	Pyridine, 3-ethynyl-5-(2S)-1-methyl-2-pyrrolidinyl- [CAS]	179120-92-4	US	5594011	Antiparkinsonian	Parkinson's disease
altretamine	1,3,5-Triazine-2,4,6-triamine, N,N,N',N',N'',N''-hexamethyl- [CAS]	645-05-6	US	3424752	Anticancer, alkylating	Cancer, ovarian
aluminium chloride hexahydrate	Aluminium chloride, hexahydrate	7446-70-0 7784-13-6			Dermatological	Hyperhidrosis

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference	Example of Therapeutic Use	Example of Indication
Aluminon		569-58-4			
Aluminum Acetate Solution		8006-13-1			
Aluminum Chlorate		15477-33-5			
Aluminum Hydroxychloride		1327-41-9			
Aluminum Potassium Sulfate		10043-67-1			
Aluminum Sodium Sulfate		10102-71-3			
alusulf	Aluminum hydroxide sulfate (Al7(OH)17(SO4)2), dodecahydrate [CAS]	61115-28-4	DE 2510663	Urological	hyperphosphatasemia
Alverine	Glycine, N-[(2S)-2-[[(3R,4R)-4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]methyl]-1-oxo-3-phenylpropyl]- [CAS]	150-59-4			
alvimopan	4H-1-Benzopyran-4-one, 2-(2-chlorophenyl)-5,7-dihydroxy-8-[3-hydroxy-1-methyl-4-piperidinyl]-, cis-(+)- [CAS]	156053-89-3	EP 657428	GI Inflammatory/bowel disorders	Ileus
alvocidib		131740-09-5		Anticancer, other	Cancer, renal
ALX-0646		146426-40-6	WO 9506638	Antimigraine	Migraine
AM-24	2,4,6-Tribromophenol	609-23-4		GI Inflammatory/bowel disorders	Crohn's disease
AM-36	1-Piperazineethanol, 4-[[5,5-bis[1,1-dimethylethyl)-4-hydroxyphenyl]methyl]-Alpha-(4-chlorophenyl)- [CAS]	199467-52-2		Neuroprotective	Unspecified
AM-477	2-Methoxyestradiol			Antiasthma	Asthma
Amantadine		768-94-5			
amantanium	1-Decanaminium, N,N-dimethyl-N-[2-[(trinitrophenyl)methyl]-, bromide [CAS]	58158-77-3	US 4288609	Antifungal	Infection, general
Ambazone		539-21-9			
Ambenonium		115-79-7			

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API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
ambrisentan	(+)-(2S)-2-[(4,6-dimethylpyrimidin-2-yl)oxy]-3-methoxy-3,3-diphenylpropanoic acid	177036-94-1			Vasodilator, peripheral	Heart failure
ambroxol	Cyclohexanol, 4-[[(2-amino-3,5-dibromophenyl)methyl]amino]-, trans- [CAS]	18683-91-5 23828-92-4	GB	1178034	COPD treatment	Bronchitis, chronic
Ambucaine		119-29-9				
Ambuphylline		5634-34-4				
Ambuside		3754-19-6				
Ambutonium Bromide		115-51-5				
amcinonide	Pregna-1,4-diene-3,20-dione, 21-(acetyloxy)-16,17-[cyclopentylidenebis(oxy)]-9-fluoro-11-hydroxy-, (11ß,16Alpha)- [CAS]	51022-69-6	DE	2437847	Antipsoriasis	
AMD-3100	1,4,8,11-Tetraazacyclotetradecane, 1,11-(1,4-phenylenebis(methylene))bis-, octahydrochloride [CAS]	155148-31-5	US	5612478	Haematological	Chemotherapy-induced injury, bone marrow, leucopenia
Amdinocillin		32887-01-7				
Amdinocillin Pivoxil		32886-97-8				
amdoxovir	1,3-Dioxolane-2-methanol, 4-(2,6-diamino-9H-purin-9-yl)- (2R-cis)- [CAS]	145514-04-1	EP	656778	Antiviral, anti-HIV	Infection, HIV/AIDS
amelubant	Carbamic acid, ((4-((3-((4-(1-(4-hydroxyphenyl)-1-methylethyl)phenoxy)methyl)phenyl)methoxy)phenyl)iminomethyl)- ethyl ester [CAS]	346735-24-8	DE	10000907	COPD treatment	Chronic obstructive pulmonary disease
Americaine	Benzenemethanaminium, N,N-dimethyl-N-[2-[2-[4-(1,1,3,3-tetramethylbutyl)phenoxy]ethoxy]ethyl]-, chloride, mixt. with ethyl 4-aminobenzoate [CAS]	129128-13-8			Formulation, inhalable, other	Pain, general
Amezinium		30578-37-1				
Amfenac		51579-82-9				
Amidephrine		3354-67-4				
Amidinomycin		3572-60-9				

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API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
	Ethanethiol, 2-[(3-aminopropyl)amino]-, dihydrogen phosphate (ester)- [CAS]	20537-88-6	EP	131500	Radio/chemoprotective	Chemotherapy-induced injury, renal
amifostine		63717-27-1				
amiglumide	Pentanoic acid, 5-[(phenylamino)-4-[(2-naphthalenylcarbonyl)amino]-5-oxo- (R)- [CAS]	119363-62-1	WO	8805774	GI inflammatory/bowel disorders	Pancreatitis
amikacin		37517-28-5			Formulation, optimized, microencapsulate	Infection, general
		39831-55-5				
Amiloride		2609-46-3				
Aminacrine		90-45-9				
aminepsine	Heptanoic acid, 7-[(10,11-dihydro-5H-dibenz[b,f]cycloheptan-5-yl)amino]- [CAS]	30272-08-3				
		57574-09-1	US	3758528	Antidepressant	
Aminitrozole		140-40-9				
Amino Acid Preparations						
Aminocaproic Acid						
aminoglutethimide	2,6-Piperidinedione, 3-(4-aminophenyl)-3-ethyl- [CAS]	125-84-8	US	3944671	Anticancer, hormonal	Cancer, breast
Aminoguanidine		79-17-4				
Aminohippurate						
Aminometradine		642-44-4				
Aminopentamide		60-46-8				
aminophylline	1H-Purine-2,6-dione, 3,7-dihydro-1,3-dimethyl-, compd. with 1,2-ethanediamine (2:1) [CAS]	317-34-0			Formulation, modified-release, other	Asthma
Aminopromazine		58-37-7				
Aminopyrine		58-15-1				
Aminoquinuride		3611-56-1				
Aminorex		2207-50-3				
amiodarone	Methanone, (2-butyl-3-benzofuranyl)[4-[2-(diethylamino)ethoxy]-3,5-diiodophenyl]- [CAS]	1951-25-3				
		19774-82-4	US	3248401	Antiarrhythmic	Arrhythmia, general
Amiphenazole		490-55-1				
Amiprilose		56824-20-5				

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API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
amisulpride	Benzamide, 4-amino-N-[1-ethyl-2-pyrrolidinyl)methyl]-5-(ethylsulfonyl)-2-methoxy- [CAS]	71675-85-9	US	4401822	Neuroleptic	Schizophrenia
Amitriptyline		50-48-6				
amitriptyline+Histamine	1-Propanamine,3-(10,11-dihydro-5H-dibenzo[a,d]cycloheptén-5-ylidene)-N,N-dimethyl- + cyclohexanone,2-(2-chlorophenyl)-2-(methylamino)				Formulation, fixed-dose combinations	Pain, neuropathic
Amitriptylinoxide		4317-14-0				
amlexanox	5H-[1]Benzopyrano[2,3-b]pyridine-3-carboxylic acid, 2-amino-7-(1-methylethyl)-5-oxo- [CAS]	68302-57-8	US	4299963	Antiasthma	Asthma
amlodipine	3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester [CAS]	111470-99-6 88150-42-9 88150-47-4	EP	89167	Antianginal	Hypertension, general
Ammoniacum		03/07/9000				
Ammonium Benzoate		1863-63-4				
Ammonium Mandelate		530-31-4				
Ammonium Salicylate		528-94-9				
Ammonium Valerate		42739-38-8				
Amobarbital		57-43-2				
Amocarzine		36590-19-9				
Amodiaquin		86-42-0				
amorolfine	Morpholine, 4-[3-[4-(1,1-dimethylpropyl)phenyl]-2-methylpropyl]-2,6-dimethyl-, cis- [CAS]	78613-35-1 78613-38-4	EP	24334	Antifungal	Infection, fungal, general
Amoscanate		26328-53-0				
amosulalol	Benzenesulfonamide, 5-[1-hydroxy-2-[[2-(2-methoxyphenoxy)ethyl]amino]ethyl]-2-methyl-, (+/-)- [CAS]	70958-86-0 86320-58-9	EP	136103	Antihypertensive, adrenergic	Hypertension, general
Amotriptheine		5585-64-8				
amoxapine	Dibenz[b,f][1,4]oxazepine, 2-chloro-11-(1-piperazinyl)- [CAS]	14028-44-5	GB	1192812	Antidepressant	Depression, general

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amoxicillin	4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[(aminohydroxyphenylacetyl)amino]-3,3-dimethyl-7-oxo-, [2S-[2alpha,5alpha,6[S*(]]] [CAS]	26787-78-0 61336-70-7			Formulation, modified-release, other	Infection, general
amoxicillin+potassium clavulan			GB	1508977	Formulation, fixed-dose combinations	Infection, respiratory tract, general
AMPAlex	Piperidine, 1-(6-quinoxalinylcarbonyl)- [CAS]	74468-00-4 154235-83-3	US	566409	Psychostimulant	Attention deficit disorder
Amphetamine		300-62-9				
Amphetaminil		17590-01-1				
amphotericin B	Amphotericin B compd. with (3ß)-cholest-5-en-3-yl hydrogen sulfate (1:1) [CAS]	120895-52-5 1397-89-3	US	4822777	Formulation, optimized, liposomes	Infection, general
ampicillin	4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo-, [2S-[2alpha,5alpha,6S*(S*)]]	69-53-4 7177-48-2			Formulation, fixed-dose combinations	Infection, general
Ampiroxicam		99464-64-9				
Ampligen		30640-92-5				
empensavir	Carbamic acid, (3-[((4-aminophenyl)sulfonyl)(2-(ethoxymethoxy)ethyl)amino]-2-hydroxy-1-(phenylmethyl)propyl)-, 1,1-dimethylethyl ester, (3S*,2R*(1R*,2S*))]- [CAS]	161814-49-9	US	5783701	Antiviral, anti-HIV	Infection, HIV/AIDS
amrinone	[3,4'-Bipyridin]-6(1H)-one, 5-amino- [CAS]	60719-84-8 75898-90-7	US	4004012	Cardiostimulant	
amrubicin	5,12-Naphthacenedione, 9-acetyl-9-amino-7,10-dideoxy-8-D-erythro-pentopyranosyloxy)-7,8,9,10-tetrahydro-6,11-dihydroxy-, hydrochloride, (7S-cis)- [CAS]	92396-36-3	EP	107486	Anticancer, antibiotic	Cancer, lung, non-small cell
amsacrine	Methanesulfonamide, N-[4-(9-acridinylamino)-3-methoxyphenyl]- [CAS]	51264-14-3			Anticancer, other	Cancer, leukaemia, acute lymphocytic

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amtolmetin guacil	Glycine, N-[[1-methyl-5-(4-methylbenzoyl)-1H-pyrrol-2-yl]acetyl]-, 2-methoxyphenyl ester [CAS]	87344-06-7	GB	2115417	Analgesic, NSAID	Arthritis, rheumatoid
Amylocaine		532-59-2				
AN-152			WO	9719954	Anticancer, antibiotic	Cancer, prostate
anabolic steroids			WO	9848612	Cardiovascular	Heart failure
Anagestone		2740-52-5				
anagrelide	Imidazo[2,1-b]quinazolin-2(3H)-one, 6,7-dichloro-1,5-dihydro-, monohydrochloride [CAS]	58579-51-4 68475-42-3	GB	1418822	Haematological	Thrombocytosis
anastrozole	1,3-Benzenediacetonitrile, Alpha,Alpha,Alpha,Alpha'-tetramethyl-5-(1H-1,2,4-triazol-1-ylmethyl)- [CAS]	120511-73-1	EP	296749	Anticancer, hormonal	Cancer, breast
Anazolene		3861-73-2				
Ancitabine		31698-14-3				
Ancrod		9046-56-4				
andolast	N-4'-[5-Tetrazolyl]-phenyl-4-(5-tetrazolyl)-benzamide	132640-22-3	EP	460083	Antiasthma	Asthma
Androisoxazole		360-66-7				
Androstenediol		521-17-5				
anecortave	21-(Acetyloxy)-17-hydroxypregna-4,9(11)-diene-3,20-dione	7753-60-8			Ophthalmological	Macular degeneration
Anethole		4180-23-8; 104-46-1 (unspecified)				
Anethole Trithione		532-11-6	US	6417205	Cardiovascular	Cardiomyopathy, ischaemic
Angiogenix						
Angiotensin		1407-47-2				
ainhydrovinblastine	Vincaleukoblastine, 3',4'-didehydro-4'-deoxy- [CAS]	38390-45-3	US	6011041	Anticancer, other	Cancer, general
anidulafungin	Echinocandin B, 1-((4R,5R)-4,5-dihydroxy-N2-((4''-pentyloxy)(1,1':4',1''-terphenyl)-4-yl)carbonyl)-L-ornithine)- [CAS]	166663-25-8	US	6334013	Antifungal	Infection, Candida, general

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API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Amileridine		144-14-9				
Aniracetam		72432-10-1				
Anisindione		117-37-3				
Anisomycin		22862-76-6				
Anisotropine Methylbromide		80-50-2				
anistreplase	Anistreplase [CAS]	81669-67-0	EP 28489		Fibrinolytic	Infarction, myocardial
Antazoline		91-75-8				
Anthiolimine		305-97-5				
Anthralin		1143-38-0				
Anthramycin		4803-27-4				
Anthrarobin		577-33-3				
anthrax inhibitor				US 6436933	Anti-infective, other	Infection, anthrax
antiangiogenic dendrimare				US 6426067	Anticancer, other	Cancer, general
Anticort	L-Ascorbic acid, mixt with 2-(diethylamino)ethyl 4-aminobenzoate monohydrochloride, disodium hydrogen phosphate, potassium benzoate and zinc sulfate (1:1) [CAS]	186646-39-9	WO 9640038		Anabolic	Cachexia
antidepressants			US 5898036		Antidepressant	Depression, general
anti-invasins			US 6303302		Antifungal	Infection, fungal, general
Antimony Potassium Tartrate		28300-74-5				
Antimony Sodium Thioglycolate		539-54-8				
Antimony Thioglycollamide		6533-78-4				
Antiprogestin	19-Norpregna-4,9-dien-3-one,(acetylphenyl)-20,20,21,21,21-pentafluoro-17-hydroxy (11ß,17Alpha) [CAS]	211254-73-8	DE 19706061		Anticancer, hormonal	Cancer, breast
Antipyrine		60-80-0				
Antipyrine Salicylate		520-07-0				
antithrombin III	Antithrombin, III [CAS]	9000-94-6 90170-80-2			Blood fraction	Antithrombin III deficiency

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anxiolytics			US	5756538	Anxiolytic	Anxiety, general
AP-521	N-P-peronyl-2-amino-1,2,3,4-tetrahydrobenzo(b)thieno[2,3-c]pyridine-3-carbamide	151227-08-6	WO	9321189	Anxiolytic	Anxiety, general
AP-5280			US	5665118	Anticancer, alkylating	Cancer, general
Apalcillin		63469-19-2				
apaziquone	1H-Indole-4,7-dione, 5-(1-aziridinyl)-3-(hydroxymethyl)-2-(3-hydroxy-1-propenyl)-1-methyl-, (E)- [CAS]	114560-48-4	WO	8706227	Anticancer, alkylating	Cancer, breast
Apazone		13539-59-8				
α-Phenylbutyramide		90-26-6				
Apocodeine		641-36-1				
apomine	Phosphonic acid, (2-(3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl)ethylidene)bis- tetrakis(1-methylethyl) ester [CAS]	126411-13-0			Anticancer, other	Cancer, prostate
apomorphine	4H-Dibenzo[de,g]quinoline-10,11-diol, 5,6,6a,7-tetrahydro-6-methyl-, hydrochloride	314-19-2 58-00-4			Formulation, transmucosal, nasal	Impotence
apraclonidine	1,4-Benzenediamine, 2,6-dichloro-N1-(4,5-dihydro-1H-imidazol-2-yl)- [CAS]	73218-79-8	US	4617199	Antiglaucoma	Glaucoma
aprepitant	3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- [CAS]	170729-80-3	US	5719147	Antiemetic	Chemotherapy-induced nausea and vomiting
aprindine	1,3-Propanediamine, N-(2,3-dihydro-1H-inden-2-yl)-N',N'-diethyl-N-(4-phenyl)-[CAS]	33237-74-0 37640-71-4	GB	1321424	Antiarrhythmic	
Aprobarbital		77-02-1				
Apronalide		528-92-7				
Aprotinin		9087-70-1				
Aptiganel		137159-92-3				
AQ4N	9,10-Anthracenedione, 1,4-bis[(2-(dimethyloxidoaminio)ethyl)amino]-5,8-dihydroxy-[CAS]	136470-65-0	US	5132327	Anticancer, other	Cancer, general
Aquavan			US	6204257	Anaesthetic, injectable	Anaesthesia

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API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
AR-116081			US	6107324	Neuroleptic	Unspecified
AR-A2	(R)-N-[5-methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide				Anxiolytic	Anxiety, general
Arachidonic Acid		506-32-1				
aranidipine	3,5-Pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-, methyl 2-oxopropyl ester- [CAS]	86780-90-7	GB	2111978	Antihypertensive, other	Hypertension, general
arbekacin	D-Streptamine, O-3-amino-3-deoxy-Alpha-D-glucopyranosyl-(1-6)-O-[2,6-diamino-2,3,4,6-tetradeoxy-Alpha-D-erythro-hexopyranosyl-(1-4)]-N1-(4-amino-2-hydroxy-1-oxobutyl)-2-deoxy-, (S)- [CAS]	51025-85-5 75282-65-4	US	4001208	Aminoglycoside antibiotic	Infection, general
Arbidol	1H-Indole-3-carboxylic acid, 6-bromo-4-((dimethylamino)methyl)-5-hydroxy-1-methyl-2-((phenylthio)methyl)-, ethylester, monohydrochloride [CAS]	131707-23-8	WO	9008135	Immunostimulant, other	Infection, Influenza virus
arbutamine	1,2-Benzenediol, 4-[1-hydroxy-2-[[4-(4-hydroxyphenyl)butyl]amino]ethyl]-, (R)- [CAS]	128470-16-6	WO	9220324	Diagnostic	Diagnosis, coronary
Arcitumomab		154361-48-5				
ardeparin	Heparin [CAS]	9005-49-6			Anticoagulant	Thrombosis, venous
arecoline	1,2,5,6-Tetrahydro-1-methyl-3-pyridine carboxylic acid methyl ester				Formulation, transdermal, patch	Alzheimer's disease
argatroban	2-Piperidinecarboxylic acid, 1-[5-[(aminoiminomethyl)amino]-1-oxo-2-[[(1,2,3,4-tetrahydro-3-methyl-8-quinolinyl)sulfonyl]amino]pentyl]-4-methyl- [CAS]	74863-84-6	EP	8746	Anticoagulant	Thrombosis, arterial
Arginine		74-79-3				
Arifio®		153259-65-5				
aripiprazole	2(1H)-Quinolinone, 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydro- [CAS]	129722-12-9	EP	367141	Neuroleptic	Schizophrenia

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API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
arofylline	1H-Purine-2,6-dione, 3-(4-chlorophenyl)-3,7-dihydro-1-propyl- [CAS]	136146-07-8	EP	435811	COPD treatment	Chronic obstructive pulmonary disease
arotinolol	2-Thiophenecarboxamide, 5-[2-[[3-[(1,1-dimethylethyl)amino]-2-hydroxypropyl]thio]-4-thiazolyl]-, (±)- [CAS]	104768-23-6 68377-92-4	US	3932400	Antihypertensive, adrenergic	Hypertension, general
Arsacetin		618-22-4				
arsenic trioxide	Arsenic oxide (As2O3) [CAS]	1327-53-3			Anticancer, other	Cancer, leukaemia, acute myelogenous
Arsphenamine		139-93-5				
Arsthinol		119-96-0				
Artether		75887-54-6				
Artefene		123407-36-3 (Z form)				
Artemether		71963-77-4				
Artemisinin		63968-64-9				
artemotil	3,12-Epoxy-12H-pyrano[4,3-j]-1,2-benzodioxepin, 10-ethoxydecahydro-3,6,9-trimethyl-, [3R-(3Alpha,5aS,6S,6aS,8aS,9Alpha,10Alpha,12S,12aR*)]- [CAS]	75887-54-6			Antimalarial	Infection, malaria
artesunate	Butanedioic acid mono-[(3R,5aS,6R,8aS,9R,10R,12R,12aR)-decahydro-3,6,9-trimethyl-3,12-epoxy-12H-pyrano[4,3-j]-1,2-benzodioxepin-10-yl]ester	88495-63-0			Formulation, transmucosal, systemic	Infection, malaria
arzoxifene	Benzo[b]thiophene-6-ol, 2-(4-methoxyphenyl)-3-(4-(2-(1-piperidinyl)ethoxy)phenoxy)- [CAS]	182133-27-3	WO	9609041	Anticancer, hormonal	Cancer, breast
AS-3201	Spiro(pyrrolizine-3,4'(1'H)-pyrrolo[1,2-a]pyrazine)-1',2,3',5(2'H)-tetrone, 2'-(4-bromo-2-fluorophenyl)methyl)-, (5R)- [CAS]	147254-64-6	EP	520320	Symptomatic antidiabetic	Diabetic complication, general
ASA	Benzoic acid, 2-(acetyloxy)- [CAS]	50-78-2 50449-07-1			Formulation, modified-release, other	Pain, general

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API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
α-Santonin		481-06-1				
Ascaridole		512-85-6				
Ascorbic Acid		50-81-7				
asenapine	1H-Dibenz[2,3:6,7]oxepino[4,5-c]pyrrole, 5-chloro-2,3a,12b-tetrahydro-2-methyl-, trans-, (Z)-2-butenedioate (1:1) [CAS]	85650-56-2	WO	9523600	Neuroleptic	Psychosis, general
asimadoline	Benzeneacetamide, N-[2-(3-hydroxy-1-pyrrolidinyl)-1-phenylethyl]-N-methyl-Alpha-phenyl-, [S-(R*,R*)]- [CAS]	153205-46-0	DE	4215213	GI inflammatory/bowel disorders	Irritable bowel syndrome
asoprisnil	11ß-[4-(Hydroxyiminomethyl)phenyl]-17ß-(methoxy-17Alpha-(methoxymethyl)estra-4,9-dien-3-one	199396-76-4	EP	0648778	Menstruation disorders	Endometriosis
Asoxime		34433-31-3				
Aspartic Acid		56-84-8				
Aspidin		584-28-1				
Aspidinol		519-40-4				
Aspirin		50-78-2				
Aspirin, Dipyridamole						
aspoxicillin	Glycinamide, N-methyl-D-asparaginyl-N-[2-carboxy-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-6-yl]-D-2-(4-hydroxyphenyl)-, [2S-(2Alpha,5Alpha,6ß)]- [CAS]	63358-49-6	GB	1533413	Penicillin, injectable	Infection, respiratory tract, general
AST-120	AST 120 [CAS]	90597-58-3			Urological	Renal failure
Astemizole		68844-77-9				
asulacrine	4-Acridinecarboxamide, 9-[[2-methoxy-4-[(methylsulfonyl)amino]phenyl]amino]-N,5-dimethyl- [CAS]	80841-47-0 80841-48-1	EP	39224	Anticancer, other	Cancer, general
AT-1015	(N'-[2-[4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-piperidinyl]ethyl]-1-formyl-4-piperidinecarboxamide monohydrochloride monohydrate					
atamestane	Androsta-1,4-diene-3,17-dione, 1-methyl- [CAS]	96301-34-7	DE	3338212	Anticancer, hormonal	Thrombosis, general Cancer, breast

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
atazanavir	2,5,6,10,13-Pentaazatetradecanedioic acid, 3,12-bis(1,1-dimethylethyl)-8-hydroxy-4,11-dioxo-9-(phenylmethyl)-6-[(4-(2-pyridinyl)phenyl)methyl]- dimethyl ester, (3S,8S,9S,12S)-, sulfate (1:1) (salt) [CAS]	229975-97-7			Antiviral, anti-HIV	Infection, HIV/AIDS
atenolol	Benzeneacetamide, 4-[2-hydroxy-3-[(1-methylethyl)amino]propoxy]- [CAS]	29122-68-7 73677-19-7	GB	1285038	Antihypertensive, adrenergic	Hypertension, general
atenolol + chlorthalidone	Benzeneacetamide, 4-[2-hydroxy-3-[(1-methylethyl)amino]propoxy]-, mixt. with 2-chloro-5-(2,3-dihydro-1-hydroxy-3-oxo-1H-isoindol-1-yl)benzenesulfonamide [CAS]	73677-19-7	US	3836671	Formulation, fixed-dose combinations	Hypertension, general
atenolol + nifedipine	Benzeneacetamide, 4-[2-hydroxy-3-[(1-methylethyl)amino]propoxy]- + 4-(2'-nitrophenyl)-2,6-dimethyl-3,5-dicarbomethoxy-1,4-dihydropyridine				Formulation, fixed-dose combinations	Hypertension, general
α-Terpineol		98-55-5				
Atevirdine		136816-75-6				
atipamezole	1H-Imidazole, 4-(2-ethyl-2,3-dihydro-1H-inden-2-yl)- [CAS]	104054-27-5	EP	183492	Reproductive/gonadal, general	Sexual dysfunction, female
atiprimod dimaleate	2-Azaspiro[4.5]decane-2-propanamine, N,N-diethyl-8,8-dipropyl, dimaleate	130065-61-1	US	5744495	Antiarthritic, immunological	Arthritis, rheumatoid
ATL-146e			US	6232297	Imaging agent	Unspecified
α-Tocopherol		59-02-9				
atomoxetine	Benzenepropanamine, N-methyl-Gamma-(2-methylphenoxy)-, (R)- [CAS]	82248-59-7 83015-26-3	EP	52492	Neurological	Attention deficit disorder
atorvastatin	1H-Pyrrole-1-heptanoic acid, 2-(4-fluorophenyl)-B,delta-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]- [CAS]	134523-03-8 134523-00-5	EP	409281	Hypolipaemic/Antiatherosclerosis	Hypercholesterolaemia
atosiban	Oxytocin, 1-(3-mercaptopropanoic acid)-2-(O-ethyl-D-tyrosine)-4-L-threonine-8-L-ornithine- [CAS]	90779-69-4	EP	112809	Labour inhibitor	Labour, preterm

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API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
atovaquone	1,4-Naphthalenedione, 2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-, trans- [CAS]	95233-18-4	EP	123238	Antifungal	Infection, Pneumocystis jiroveci
atovaquone + proguanil	1,4-Naphthalenedione,2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-,trans + N-(4-chloro-phenyl)-N-(1-methylethyl)imidiodicarbonimidic diamide				Antimalarial	Infection, malaria
atracurium	Isoquinolinium, 2,2'-[1,5-pentanediylbis[oxy(3-oxo-3,1-propanediyl)]]bis[1-[(3,4-dimethoxyphenyl)methyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl- [CAS]	64228-81-5	US	4179557	Muscle relaxant	Surgery adjunct
atrasentan	3-Pyrrolidinecarboxylic acid, 4-(1,3-benzodioxol-5-yl)-1-[2-(dibutylamino)-2-oxoethyl]-2-(4-methoxyphenyl)-, (2R,3R,4S)- [CAS]	173937-91-2	WO	9730045	Anticancer, other	Cancer, prostate
Atrial Natriurstic Peptide		85637-73-6				
Atrolactamide		2019-68-3				
Atropine		51-55-8				
Augmentin		74469-00-4			Formulation, modified-release, other	Infection, respiratory tract, general
auranofin	Gold, (1-thio-ß-D-glucopyranose 2,3,4,6-tetraacetato-S)(triethylphosphine)-[CAS]	34031-32-8	US	3708579	Antiarthritic, other	Arthritis, rheumatoid
Aurothioglucose		12192-57-3				
avasimibe	Sulfamic acid, [[2,4,6-tris(1-methylethyl)phenyl]acetyl]-, 2,6-bis(1-methylethyl)phenyl ester [CAS]	166518-60-1	US	5491172	Hypolipaemic/Antiatherosclerosis	Atherosclerosis
Avobenzone		70356-09-1				
AWD-12-281	AWD 12-281 [CAS]	257892-33-4			Antiallergic, non-asthma	Rhinitis, allergic, general
Azacitidine		320-67-2				
Azacyclonol		115-46-8				
azanidazole	2-Pyrimidinamine, 4-[2-(1-methyl-5-nitro-1H-imidazol-2-yl)ethenyl]-,(E)- [CAS]	62973-76-6	US	3882105	Antibacterial, other	Infection, trichomoniasis

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azapropazone	1H-Pyrazolo[1,2-a][1,2,4]benzotriazine-1,3(2H)-dione, 5-(dimethylamino)-9-methyl-2-propyl- [CAS]	13539-59-8	FR	1440629	Anti-inflammatory	
Azaserine		115-02-6				
azasetron	2H-1,4-Benzoxazine-8-carboxamide, N-1-azabicyclo[2.2.2]oct-3-yl-6-chloro-3,4-dihydro-4-methyl-3-oxo-, monohydrochloride- [CAS]	123040-16-4 123040-94-8 123040-96-0 123040-69-7	EP	313393	Antiemetic	Nausea and vomiting, general
Azatadine		3964-81-6				
azathioprine	6-[(1-Methyl-4-nitro-1H-imidazol-5-yl)thio]-1H-purine	446-86-6			Formulation, oral, other	Transplant rejection, bone marrow
AZD-4282	glycine				Analgesic, other	Pain, neuropathic
AZD-6140	3,4 Difluorophenylcyclopropylamine				Antithrombotic	Thrombosis, arterial
azelaic acid	Nonanedioic acid [CAS]	123-99-9			Antiacne	Acne
azelastine	1(2H)-Phthalazinone, 4-[(4-chlorophenyl)methyl]-2-(hexahydro-1-methyl-1H-azepin-4-yl)-, monohydrochloride [CAS]	58581-89-8 79307-93-0	GB	1377231	Antiasthma	Asthma
azelnidipine	3,5-Pyridinedicarboxylic acid, 2-amino-1,4-dihydro-6-methyl-4-(3-nitrophenyl)-, 3-[1-(diphenylmethyl)-3-azetidinyl] 5-(1-methylethyl)ester, (+/-)- [CAS]	123524-52-7	EP	266922	Antihypertensive, other	Hypertension, general
Azidamfenicol		13838-08-9				
Azidocillin		17243-38-8				
Azimilide		149908-53-2				
Azintamide		1830-32-6				
azithromycin	9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin-A	76801-85-9 83905-01-5 92395-24-9	US	4328334	Macrolide antibiotic	Infection, respiratory tract, lower
aziocillin	4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[[[(2-oxo-1-imidazolidinyl)carbonyl]amino]phenylacetyl]amino]-, [2S-[2.alpha.,5Alpha,6ß(S*)]]- [CAS]	37091-65-9 37091-66-0	GB	1392849	Penicillin, injectable	Infection, general

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Azosemide		27589-33-9				
aztreonam	Propanoic acid, 2-[[1-(2-amino-4-thiazolyl)-2-[(2-methyl-4-oxo-1-sulfo-3-azetidinyl)amino]-2-oxoethylidene]amino]oxy]-2-methyl-, [2S-[2Alpha,3[(Z)]]-[CAS]	104184-69-2 78110-38-0	GB	2071650	Beta-lactam antibiotic	Infection, general
azulene	Sodium 5-Isopropyl-3,8-dimethyl-1-azulene sulfonate	6223-35-4	EP	88958	Formulation, modified-release, other	Inflammation, general
bacampicillin	4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo-, 1-[(ethoxycarbonyl)oxy]ethyl ester, [2S-[2Alpha,5Alpha,6[(S*)]]- [CAS]	37661-08-8 50972-17-3	GB	1363506	Penicillin, oral	Infection, general
Bacitracin		1405-87-4				
baclofen	ß-(Aminomethyl)-4-chlorobenzenepropanoic acid [CAS]	1134-47-0			Formulation, implant	Spastic paralysis
Balcalein		491-67-8				
balofloxacin	3-Quinolinecarboxylic acid, 1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-[3-(methylamino)-1-piperidinyl]-4-oxo- [CAS]	127294-70-6	EP	342675	Quinolone antibacterial	Infection, urinary tract
balsalazide	Benzoic acid, 5-[[4-[[(2-carboxyethyl)amino]carbonyl]phenyl]azo]-2-hydroxy-, (E)- [CAS]	80573-04-2	US	4412992	GI inflammatory/bowel disorders	Colitis, ulcerative
bambuterol	Carbamic acid, dimethyl-, 5-[2-[(1,1-dimethylethyl)amino]-1-hydroxyethyl]-1,3-phenylene ester, monohydrochloride [CAS]	81732-46-9 81732-65-2	EP	43807	Antiasthma	Asthma
Bamethan		3703-79-5				
Bamifylline		2016-63-9				
Bamipine		4945-47-5				
Barbital		57-44-3				
barnidipine	3,5-Pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-, methyl-1-(phenylmethyl)-3-pyrrolidinyl ester, [S-(R*,R*)]-	104713-75-9 104757-53-1 71863-56-4	US	4220649	Antihypertensive, other	Hypertension, general

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BAS-118	N-Methyl-3-[2-(2-naphthyl)acetylamino]benzamide			Antibacterial, other	Infection, Helicobacter pylori
Basic Aluminum Carbonate, Gel		1339-92-0			
Basiliximab		179045-86-4			
Batimastat		130370-60-4			
Batroxobin		9039-61-6			
Bay-41-2272	5-cyclopropyl-2-[1(2-fluoro-benzyl)-1H-pyrazolo[3,4-b]pyridine-3-yl]pyrimidin-4-ylamine			Male sexual dysfunction	Sexual dysfunction, male, general
Bay-41-8543	2-[1-(2-Fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-5-(4-mopholinyl)pyrimidine-4,6-diamine			Cardiovascular	Unspecified
BAY-43-9006	N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl)urea			Anticancer, other	Cancer, liver
BAY-57-1293	N-[6(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)phenyl]acetamide			Antiviral, other	Infection, herpes simplex virus
bezedoxifen	TSE 424 [CAS]	198481-33-3	EP 802183	Osteoporosis treatment	Osteoporosis
β-Benzalbutyramide		7236-47-7			
BBR-3464	Platinum(4+), hexaamminedichlorobis[μ-(1,6-hexanediamine-N:N')]tri- stereoisomer, tetranitrate [CAS]	172903-00-3	US 5744497	Anticancer, alkylating	Cancer, lung, non-small cell
BBR-3576			US 5519029	Anticancer, antibiotic	Cancer, prostate
BBR-3610			US 6060616	Anticancer, alkylating	Cancer, general
β-Carotene		7235-40-7			
BCH-1868	(+)-2,R-dihydroxyphosphinyl-5-(9-guanin-9-yl-methyl)tetrahydrofuran			Anticancer, antimetabolite	Cancer, general
Bebeerine		477-60-1			
Beclamide		501-68-8			

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beclomesasone	Pregna-1,4-diene-3,20-dione, 9-chloro-11b,17,21-trihydroxy-16b-methyl, [CAS]	5534-09-8 4419-39-0	WO	0008132	Formulation, inhalable, solution	Asthma
Befloxatone		134564-82-2				
befunolol	Ethanone, 1-[7-[2-hydroxy-3-[(1-methylethyl)amino]propoxy]-2-benzofuranyl]-[CAS]	39543-79-8 39552-01-7			Antiglaucoma	
Bemegride		64-65-3				
Benactyzine		302-40-9				
benazepril	1H-1-Benzazepine-1-acetic acid, 3-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-2,3,4,5-tetrahydro-2-oxo-, [S-(R*,R*)]-[CAS]	86541-74-4 86541-75-5 86541-78-8	EP	72352	Antihypertensive, renin system	Hypertension, general
bencyclane	1-Propanamine, N,N-dimethyl-3-[[1-(phenylmethyl)cyclohexyl]oxy]-, (E)-2-butenedioate (1:1) [CAS]	14286-84-1 2179-37-3	WO	9829409	Vasodilator, peripheral	
bendazac	L-Lysine, monoll[1-(phenylmethyl)-1H-indazol-3-yl]oxy]acetate] [CAS]	61919-14-4 20187-55-7	GB	2081708	Ophthalmological	
Bendroflumethiazide		73-48-3				
Benexate		78718-25-9				
benfluorex	Ethanol, 2-[[1-methyl-2-[3-(trifluoromethyl)phenyl]ethyl]amino]-, benzoate (ester) [CAS]	23602-78-0 23642-66-2	GB	1175516	Hypolipaemic/Antiatherosclerosis	
Benfotiamine		22457-89-2				
Benfurodil		3447-95-8				
benidipine	3,5-Pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-, methyl 1-(phenylmethyl)-3-piperidinyl ester, monohydrochloride (R*,R*)-(+/-)-[CAS]	105979-17-7 91599-74-5	EP	63365	Antihypertensive, other	Hypertension, general
Benorylate		5003-48-5				
Benoxaprofen		67434-14-4				
Benoxinate		99-43-4				
Benperidol		2062-84-2				
Benproperine		2156-27-6				
Benserazide		322-35-0				

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API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
bentazepam	2H-[1]Benzothieno[2,3-e]-1,4-diazepin-2-one, 1,3,6,7,8,9 hexahydro-5-phenyl[CAS]	29462-18-8	DE	2065276	Anxiolytic	
Bentironide		37106-97-1				
Bentoquatam		1340-69-8				
Benzalkonium		8001-54-5				
Benzarone		1477-19-6				
benzbromarone	Methanone, (3,5-dibromo-4-hydroxyphenyl)(2-ethyl-3-benzofuranyl)-[CAS]	3562-84-3	US	3012042	Antigout	
Benzethonium		121-54-0				
Benzetimide		14051-33-3				
Benzilonium		1050-48-2				
Benziodarone		68-90-6				
benznidazole	N-benzyl-2-nitroimidazole-1-acetamide	22994-85-0	GB	1138529	Protozoacide	
benzocaine	Benzoic acid, 4-amino-, ethyl ester	94-09-7			Formulation, fixed-dose combinations	Pain, musculoskeletal
Benzoctamine		17243-39-9				
Benzonatate		104-31-4				
Benzoxonium Chloride		19379-90-9				
benzoyl peroxide	Peroxide, dibenzoyl [CAS]	94-36-0			Formulation, other	Acne
Benzoylpaas		13898-58-3				
Benzphetamine		156-08-1				
Benzpiperylon		53-89-4				
Benzquinamide		63-12-7				
Benzthiazide		91-33-8				
Benztropine		132-17-2				
benzydamine	1-Propanamine, N,N-dimethyl-3-[[1-(phenylmethyl)-1H-indazol-3-yl]oxy]-, [CAS]	132-69-4 642-72-8			Stomatological, reproductive/gonadal, anti-inflammatory	
Benzyl Benzoate		120-51-4				
Benzylhydrochlorothiazide		1824-50-6				
Benzylmorphine		14297-87-1				

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API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Bephenium Hydroxynaphthoate		3818-50-6				
bepotastine	1-Piperidinebutanoic acid, 4-((4-chlorophenyl)-2-pyridinylmethoxy)-, (S)-, monobenzenesulfonate [CAS]	190786-44-8 190786-43-7	WO	9829409	Antiallergic, non-asthma	Allergy, general
bepridil	1-Pyrrolidineethanamine, ß-[(2-methylpropoxy)methyl]-N-phenyl-N-(phenylmethyl)- [CAS]	64706-54-3 74764-40-2 74764-75-3	EP	146155	Antianginal	Angina, general
beraprost	1H-Cyclopenta[b]benzofuran-5-butanoic acid, 2,3,3a,8b-tetrahydro-2-hydroxy-1-(3-hydroxy-4-methyl-1-octen-6-ynyl)- [CAS]	88475-69-8 88430-50-6	US	4474802	Prostaglandin	Peripheral vascular disease
Berberine		2086-83-1				
Bergapten		484-20-8				
Bermoprofen		78499-27-1				
Besipirdine		119257-34-0				
betahistine	2-Pyridineethanamine, N-methyl-, dihydrochloride	5579-84-0 5638-76-6			Formulation, modified-release, <=24hr	Meniere's disease
betaine	Betaine- [CAS]	107-43-7			Metabolic and enzyme disorders	Homocystinuria
betamethasone	Pregna-1,4-diene-3,20-dione, 9-fluoro-11,17,21-trihydroxy-16-methyl-, (11ß,16ß)- [CAS]	378-44-9			Formulation, dermal, topical	Psoriasis
Betamipron		3440-28-6				
Betasine		3734-24-5				
betaxolol	2-Propanol, 1-[4-[2-(cyclopropylmethoxy)ethyl]phenoxy]-3-[(1-methylethyl)amino]- [CAS]	63659-18-7 63659-19-8	US	4252984	Antihypertensive, adrenergic	Hypertension, general, glaucoma
Betazole		105-20-4				
Bethanechol		590-63-6				
Bethanidine		55-73-2				
Betoxycaine		3818-62-0				
ß-Eucaine		500-34-5				
bevantolol	2-Propanol, 1-[[2-(3,4-dimethoxyphenyl)ethyl]amino]-3-(3-methylphenoxy)- [CAS]	42864-78-8 59170-23-9	US	3857891	Antihypertensive, adrenergic	Hypertension, general
Bevonium		5205-82-3				

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bexarotene	Benzoic acid, 4-[1-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)ethenyl]- [CAS]	153559-49-0	WO	9321146	Anticancer, other	Cancer, lymphoma, T-cell
bezafibrate	Propanoic acid, 2-[4-[2-[[4-chlorobenzoyl]amino]ethyl]phenoxy]-2-methyl- [CAS]	41859-67-0	GB	1352264	Hypolipaemic/Antiatherosclerosis	
Beziramide		15301-48-1				
BG-9928		166374-48-7			Cardiostimulant	Heart failure
BIA-2-024	10,11-dihydro-10-hydroxyimino-5H-dibenz/b,f/azepine-5-carboxamide	199597-15-4	WO	9745416	Antiepileptic	Epilepsy, general
BIA-2-093	(S)-(+)-10-acetoxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide- [CAS]	236385-14-5			Antiepileptic	Epilepsy, general
BIA-3-202	1-(3,4-dihydroxy-5-nitrophenyl)-2-phenyl-ethanone	274925-86-9	EP	1010688	Antiparkinsonian	Parkinson's disease
Bialamicol		493-75-4				
biapenem	5H-Pyrazolo[1,2-a][1,2,4]triazol-4-ium, 6-[[2-carboxy-6-(1-hydroxyethyl)-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-en-3-yl]thio]-6,7-dihydro-, hydroxide, inner salt, [4R-[4Alpha,5a,6b(R*)]]- [CAS]	120410-24-4	EP	289801	Beta-lactam antibiotic	Infection, beta-actamase resistant
Bibenzonium		15585-70-3				
Bibrocathol		6915-57-7				
bicalutamide	Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-, (+/-)- [CAS]	90357-06-5	EP	100172	Anticancer, hormonal	Cancer, prostate
bicifadine	3-Azabicyclo[3.1.0]hexane, 1-(4-methylphenyl)-, (+/-)- [CAS]	66504-75-4 71195-57-8	DE	2740662	Analgesic, other	Pain, general
			US	6294585	Dermatological	Unspecified
Bidisomide		1160078-65-0				
Bietamiverine		479-81-2				
Bietanautine		6688-11-5				

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API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Betaserpine		53-18-9				
bifemelane	1-Butanamine, N-methyl-4-[2-(phenylmethyl)phenoxy]-, hydrochloride [CAS]	62232-49-6	GB	1512680	Cognition enhancer	Attention deficit disorder
		90293-01-9				
Bifluranol		34633-34-6				
bifonazole	1H-Imidazole, 1-[(1,1'-biphenyl)-4-ylphenylmethyl]- [CAS]	60628-96-8				
		60629-08-5	US	4118487	Antifungal	Infection, fungal, general
		60629-09-6				
bimeloprost	5-Heptenamide, 7-(3,5-dihydroxy-2-(3-hydroxy-5-phenyl-1-pentenyl)cyclopentyl)-N-ethyl (1R-(1Alpha(Z)2b(1E,3S,3Alpha,5Alpha)) [CAS]	155206-00-1	US	5688819	Prostaglandin	Glaucoma
bimoclomol	N-[2-hydroxy-3-(1-piperidinyl)propoxy]-3-pyridinecarboximidoyl chloride, (Z)-2-butenedioate (1:1)	130493-04-8	US	5147874	Symptomatic antidiabetic	Neuropathy, diabetic
bimosiamose	(1,1'-Biphenyl)-3-acetic acid, 3',3''-(4,6-hexanediylbis(6-alpha-D-mannopyranosyloxy)), [CAS]	187269-40-5	US	5444080	Antiasthma	Asthma
Binfibrastis		69047-39-8				
binodenoson	Adenosine, 2-((cyclohexylmethylene)hydrazino)- [CAS]	144348-08-3			Vasodilator, coronary	Diagnosis, coronary
Biomed-101			US	6423744	Anticancer, other	Cancer, renal
Biotin		58-85-5				
Biperiden		514-65-8				
biricodar	2-Piperidinecarboxylic acid, 1-(oxo(3,4,5-trimethoxyphenyl)acetyl)-,4-(3-pyridinyl)-1-(3-(3-pyridinyl)propyl)butyl ester, (S)-, 2-hydroxy-1,2,3-propanetricarboxylate (1:2) [CAS]	174254-13-8			Radio/chemosensitizer	Cancer, breast
		159987-94-1				
birpiperone	1-Butanone, 1-(4-fluorophenyl)-4-(3,4,6,7,12,12a-hexahydropyrazino[1',2':1,5]pyrido[3,4-b]indol-2(1H)-yl)- [CAS]	42021-34-1	DE	2333922	Neuroleptic	
Bisacodyl		603-50-9				

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Bisantrene		78186-34-2				
Bisbentiamine		2667-89-2				
Bisdequalinium		52951-36-7				
Bismuth Aluminate		12284-76-3				
Bismuth Butylthiolaurate		53897-25-9				
Bismuth Ethyl Camphorate		52951-37-8				
Bismuth Iodosubgallate		138-58-9				
Bismuth Sodium Iodide		53778-50-0				
Bismuth Sodium Triglycollamate		5798-43-6				
Bismuth Subcarbonate		5892-10-4				
Bismuth Subgallate		22650-86-8				
Bismuth Subnitrate		1304-85-4				
Bismuth Subsalicylate		14882-18-9				
Bismuth Tribromophenate		5175-83-7				
bisoprolol	2-Propanol, 1-[4-[[2-(1-methylethoxy)ethoxy]methyl]phenoxy]-3-[(1-methylethyl)amino]- [CAS]	104344-23-2 66722-44-9	GB	1532380	Antihypertensive, adrenergic	Heart failure
bisoprolol + HCTZ	2-Propanol, 1-[4-[[2-(1-methylethoxy)ethoxy]methyl]phenoxy]-3-[(1-methylethyl)amino] mixd. with 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide				Formulation, fixed-dose combinations	Hypertension, general
bisoprolol+trichloromethiazide	2-Propanol, 1-[4-[[2-(1-methylethoxy)ethoxy]methyl]phenoxy]-3-[(1-methylethyl)amino] mixd. with 6-chloro-3-(dichloromethyl)-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide				Formulation, fixed-dose combinations	Hypertension, general

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API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Bisoxatin		14008-48-1				
Bithionol		97-18-7				
Bitolterol		30392-40-6				
Bitoscanate		4044-65-9				
BL-3875			WO	0218378	Anti-Inflammatory	Unspecified
bleomycin	Bleomycin [CAS]	11056-06-7 9041-93-4			Formulation, transdermal, enhanced	Cancer, head and neck
blonanserin	Cycloocta[b]pyridine, 2-(4-ethyl-1-piperazinyl)-4-(4-fluorophenyl)-5,6,7,8,9,10-hexahydro- [CAS]	132810-10-7	EP	385237	Neuroleptic	Schizophrenia
BMS-184476			EP	639577	Anticancer, other	Cancer, breast
BMS-387032	cis-(+/-)-2-(Ethylthio)-5,7-dihydroxy-8-(3-hydroxy-1-methyl-4-piperidinyl)-4H-1-benzopyran-4-one		WO	9742949	Anticancer, other	Cancer, general
BN-82451	4-[2-(aminomethyl)-1,3-thiazol-4-yl]-2,6-di-tert-butylphenol, dihydrochloride				Neuroprotective	Unspecified
BNP-7787	Ethanesulfonic acid, 2,2'-dithiobis-, disodium salt [CAS]	16208-51-8			Radio/chemoprotective	Chemotherapy-Induced nausea and vomiting
BO-653	5-Benzofuranol, 4,6-bis(1,1-dimethylethyl)-2,3-dihydro-2,2-dipentyl- [CAS]	157360-23-1	WO	9408930	Hypolipaemic/Antiatherosclerosis	Atherosclerosis
Bolandiol		19793-20-5				
Bolasterone		1605-89-6				
Boldenone		846-48-0				
bopindolol	2-Propanol, 1-[(1,1-dimethylethyl)amino]-3-[(2-methyl-1H-indol-4-yl)oxy]-, benzoate (ester), (+/-)- [CAS]	62658-63-3 82857-38-3	US	4340541	Antihypertensive, adrenergic	Hypertension, general
Bornyl Chloride		464-41-5				
Bornyl Salicylate		560-88-3				
bortezomib	Boronic acid, [(1R)-3-methyl-1-[[(2S)-1-oxo-3-phenyl-2-[(pyrazinylcarbonyl)amino]propyl]amino]butyl]- [CAS]	179324-69-7	US	6271199	Anticancer, other	Cancer, myeloma

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API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
bosentan	Benzenesulfonamide, 4-(1,1-dimethylethyl)-N-[6-(2-hydroxyethoxy)-5-(2-methoxyphenoxy)[2,2'-bipyrimidin]-4-yl]- [CAS]	147536-97-8	EP	632259	Vasodilator, peripheral	Hypertension, pulmonary
BP2.94	Phenol, 2-[[[(R)-2-(1H-imidazol-4-yl)-1-[(methylphenylmethoxy)methyl]- [CAS]	136191-80-3	WO	9117146	Respiratory	Rhinitis, general
BP4.997	N-(4-(4-(2-methoxyphenyl)-1-piperazinyl)butyl)naphthalene-2-carboxamide		EP	779284	Dependence treatment	Addiction, cocaine
β-Propiolactone		57-57-8				
Bradycor		1406861-97-8				
Brain Natriuretic Peptide		1144771-18-0				
Brallobarbital		561-86-4				
bresofensine	8-Azabicyclo[3.2.1]octane-2-carboxaldehyde, 3-(3,4-dichlorophenyl)-8-methyl-, O-methyloxime, (1R-(1Alpha,2[(E),3Alpha),5Alpha))- [CAS]	171655-91-7	WO	9528401	Antiparkinsonian	Parkinson's disease
Brequinar		96187-53-0				
Bretylium		61-75-6				
Brilliant Green		633-03-4				
brimonidine	6-Quinoxalinamine, 5-bromo-N(4,5-dihydro-1H-imidazol-2-yl)- [CAS]	59803-98-4	DE	2538620	Antiglaucoma	Glaucoma
brinzolamide	2H-Thieno[3,2-e]-1,2-thiazine-6-sulfonamide, 4-(ethylamino)-3,4-dihydro-2-(3-methoxypropyl)-, 1,1-dioxide, (R)- [CAS]	138890-62-7	US	5378703	Antiglaucoma	Glaucoma
brivudin	Uridine, 5-(2-bromoethenyl)-2'-deoxy- (E)- [CAS]	69304-47-8			Antiviral, other	Infection, varicella zoster virus
Brodimoprim		56518-41-3				
Bromazepam		1812-30-2				
bromfenac	Benzeneacetic acid, 2-amino-3-(4-bromobenzoyl)- [CAS]	91714-93-1 91714-94-2			Formulation, mucosal, topical	Inflammation, ocular
Bromhexine		3572-43-8				
Bromindione		1146-98-1				
Bromisovalum		496-67-3				

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API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Bromocriptine		25614-03-3				
Bromodiphenhydramine		118-23-0				
Bromoform		75-25-2				
Bromperidol		4093-35-0				
Bromosalicylchloranilide		3679-64-9				
bromperidol	1-Butanone, 4-[4-(4-bromophenyl)-4-hydroxy-1-piperidinyl]-1-(4-fluorophenyl)- [CAS]	10457-90-6	US	3438991	Neuroleptic	Psychosis, general
Bromphenirамine		86-22-6				
Broparoestrol		479-68-5				
Bropirimine		56741-95-8				
brostallicin	4-(2-Bromoacrylamido)-N''-(2-guanidinoethyl)-1,1',1'',1''-tetramethyl-N,4':N',4'':N'',4'''-quater-(pyrrole-2-carboxamide) [CAS]				Anticancer, other	Cancer, general
brotizolam	6H-Thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine, 2-bromo-4-(2-chlorophenyl)-9-methyl- [CAS]	57801-81-7	US	4094984	Hypnotic/Sedative	
Brovincamine		57475-17-9				
Broxuridine		59-14-3				
Broxyquinoline		521-74-4				
Brucine		357-57-3				
β-Sitosterol		83-46-5				
Bucetin		1083-57-4				
Bucillamine		65002-17-7				
Bucindolol		71119-11-4				
budiodisine	Adenosine, N-(1-oxobutyl)-, cyclic 3',5'-(hydrogen phosphate) 2'-butanoate [CAS]	382-74-3	JP	51113896	Cardiostimulant	Wound healing
Buclizine		82-95-1				
Buclosamide		575-74-6				
Bucolome		841-73-6				
bucricaine	9-Acridinamine, N-butyl-1,2,3,4-tetrahydro-, monohydrochloride [CAS]	82638-29-0			Anaesthetic, local	

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API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Bucumolol		58409-59-9				
budesonide	Pregna-1,4-diene-3,20-dione, 16,17-[butylidenebis(oxy)]-11,21-dihydroxy-, (11ß,16Alpha)- [CAS]	51333-22-3	GB	1429922	Antiasthma	Asthma
budesonide + formoterol	Pregna-1,4-diene-3,20-dione, 16,17-[butylidenebis(oxy)]-11,21-dihydroxy-,(11ß,16Alpha) + formamide, N-[2-hydroxy-5-[1-hydroxy-2-[[2-(4-methoxyphenol)-1-methylethyl]amino]ethyl]phenyl]-(R*,R*)-(±)				Formulation, fixed-dose combinations	Asthma
budipine	Piperidine, 1-(1,1-dimethylethyl)-4,4-diphenyl- [CAS]	57982-78-2 63661-61-0	DE	2825322	Antiparkinsonian	Parkinson's disease
Budralazine		36798-79-5				
Bufeniode		22103-14-6				
Bufetolol		53684-49-4				
bufexamac	p-butoxyacetohydroxamic acid	2438-72-4	US	3479396	Anti-inflammatory	
bufiomadil	1-Butanone, 4-(1-pyrrolidinyl)-1-(2,4,6-trimethoxyphenyl)- [CAS]	35543-24-9 55837-25-7	GB	1325192	Vasodilator, peripheral	
Buformin		692-13-7				
Bufuralol		54340-62-4				
Bumadizon		3583-64-0				
bumetanide	Benzoic acid, 3-(aminosulfonyl)-5-(butylamino)-4-phenoxy- [CAS]	28395-03-1	US	3806534	Antihypertensive, diuretic	Hypertension, general
bunaftine	1-Naphthalenecarboxamide, N-butyl-N-[2-(diethylamino)ethyl]- [CAS]	32421-46-8	DE	2009894	Antiarrhythmic	
Bunamiodyl Sodium		1923-76-8				
bunazosin	1H-1,4-Diazepine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)hexahydro-4-(1-oxobutyl)- [CAS]	52712-76-2 80755-51-7	GB	1398455	Antihypertensive, adrenergic	Hypertension, general
bunitrolol	Benzonitrile, 2-[3-[(1,1-dimethylethyl)amino]-2-hydroxypropoxy]- [CAS]	34915-68-9	US	3940489	Antihypertensive, adrenergic	
bupivacaine	2-Piperidinecarboxamide, 1-butyl-N-(2,6-dimethylphenyl)- [CAS]	38396-39-3 2180-92-9			Formulation, modified-release, >24hr	Anaesthesia
Bupranolol		14556-46-8				

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buprenorphine	6,14-Ethenomorphinan-7-methanol, 17-(cyclopropylmethyl)-Alpha-(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-3-hydroxy-6-methoxy-Alpha-methyl-, [5Alpha,7Alpha(S)]- [CAS]	52485-79-7 53152-21-9	US	3433791	Analgesic, other	
bupropion	1-Propanone, 1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-, (+/-)- [CAS]	31677-93-7 34911-55-2	US	4425363	Antidepressant	Depression, general
Buramates		4663-83-6				
buserelin	Luteinizing hormone-releasing factor (pig), 5-[O-(1,1-dimethylethyl)-D-serine]-9-(N-ethyl-L-prolinamide)-10-deglycinamide- [CAS]	57982-77-1 68630-75-1	GB	1523623	Releasing hormones	Cancer, prostate
buspirone	8-Azaspiro[4.5]decane-7,9-dione, 8-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-[CAS]	36505-84-7	EP	276536	Anxiolytic	Anxiety, general
busulfan	1,4-Butanediol, dimethanesulfonate [CAS]	55-98-1			Formulation, optimized, microparticles	Cancer, general
busulfan	1,4-Butanediol, dimethanesulfonate- [CAS]	55-98-1			Formulation, parenteral, other	Cancer, leukaemia, acute myelogenous
Butabarbital		143-81-7				
Butacaine		149-16-6				
Butacetin		2109-73-1				
Butalamine		22131-35-7				
Butalbital		77-26-9				
Butallylonal		1142-70-7				
butamben	4-Aminobenzoic acid butyl ester [CAS]	94-25-7			Formulation, modified-release, other	Pain, cancer
butamirate	Benzeneacetic acid, Alpha-ethyl-, 2-[2-(diethylamino)ethoxy]ethylester, 2-hydroxy-1,2,3-propanetricarboxylate (1:1) [CAS]	18109-80-3 18109-81-4			Antitussive	Cough
Butanilicaine		3785-21-5				
Butaperazine		653-03-2				
Butaverine		55837-14-4				
Butazolamide		16790-49-1				
Butedronic Acid		51395-42-7				

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butenafine	1-Naphthalenemethanamine, N-((4-(1,1-dimethylethyl)phenyl)methyl)-N-methyl- [CAS]	101827-46-7 101828-21-1	EP	164697	Antifungal	Infection, dermatological
Butethal		77-28-1				
Butethamate		14007-64-8				
Butethamine		2090-89-3				
Buthalital		510-90-7				
Buthiazide		2043-38-1				
Butibufen		55837-18-8				
Butidrine		1506-12-3				
butobendine	benzoic acid, 3,4,5-trimethoxy-, 1,2-ethanediylbis[(methylimino)(2-ethyl-2,1-ethanediyl)] ester, [S-(R*,R*)]- [CAS]	55769-64-7 55769-65-8	US	4021473	Antiarrhythmic	Arrhythmia, general
butoconazole	1H-Imidazole, 1-[4-(4-chlorophenyl)-2-[(2,6-dichlorophenyl)thio]butyl]-, (+/-)- [CAS]	64872-76-0 64872-77-1	GB	1567431	Antifungal	Infection, Candida, general
Butoctamide		32838-26-9				
Butofilolol		64552-17-6				
butorphanol	Morphinan-3,14-diol, 17-(cyclobutylmethyl)-, [S-(R*,R*)]-2,3-dihydroxybutanedioate (1:1) (salt) [CAS]	42408-82-2 58786-99-5	GB	1412129	Analgesic, other	
Butoxycaine		3772-43-8				
Butriptyline		35941-65-2				
Butropium		29025-14-7				
Buzepide		3691-21-2				
BVT-5182			WO	0208178	Anorectic/Antiobesity	Obesity
BXT-51072	2H-1,2-Benzoselenazine, 3,4-dihydro-4,4-dimethyl- [CAS]	173026-17-0			GI inflammatory/bowel disorders	Colitis, ulcerative
C-1311	6H-Imidazo[4,5,1-de]acridin-6-one, 5-[[2-(diethylamino)ethyl]amino]-8-hydroxy-, 2HCl, 2H2O				Anticancer, other	Cancer, general
cabergoline	Ergoline-8-carboxamide, N-[3-(dimethylamino)propyl]-N-[(ethylamino)carbonyl]-6-(2-propenyl)-, (8ß)- [CAS]	81409-90-7 85329-89-1	GB	2103603	Antiprolactin	Galactorrhoea

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API Generic Name	API Chemical Name	CAS No.	Patent Reference	Example of Therapeutic Use	Example of Indication
Cabergoline		81409-90-7			
Cacodylic Acid		75-60-5			
Cactinomycin		8052-16-2			
cadexomer iodine	Cadexomer iodine [CAS]	94820-09-4		Anti-Infective, other	Ulcer, venostasis
Cadmium Salicylate		19010-79-8			
Cadralazine		64241-34-5			
Cafaminol		30924-31-3			
caffeine	1,2,3,-Propanetricarboxylic acid, 2-hydroxy; mixt. with 3,7-dihydro-1,3,7-trimethyl-1H-purine-2,6-dione [CAS]	69-22-7 58-08-2		Respiratory	Apnoea
Calcifediol		19356-17-3			
Calcipotriene		112965-21-6			
calcipotriol	9,10-Secochola-5,7,10(19),22-tetraene-1,3,24-triol, 24-cyclopropyl-, (1Alpha,3ß,5Z,7E,22E)- [CAS]	112965-21-6	WO 8700834	Antipsoriasis	Psoriasis
calcipotriol+betamethasone	9,10-Secochola-5,7,10(19),22-tetraene-1,3,24-triol, 24-cyclopropyl-, (1Alpha,3ß,5Z,7E,22E) + Pregna-1,4-diene-3,20-dione, 9-chloro-11ß,17,21-trihydroxy-16ß-methyl, 17,21-dipropionate			Formulation, fixed-dose combinations	Psoriasis
calcitriol	9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol, (1Alpha,3ß,5Z,7E)- [CAS]	32222-06-3		Antipsoriasis	Psoriasis
Calcium 3-Aurothio-2-propanol-1-sulfonate		5743-29-3			
Calcium Acetylsalicylate		69-46-5			
Calcium Bromoisobutionate		38659-28-8			
Calcium Carbonate		471-34-1			
Calcium Gluconate		299-28-5			
Calcium Glycerophosphate		27214-00-2			

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API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
calcium hopantothenate	Calcium D-(+)-4-(2,4-dihydroxy-3,3-dimethylbutyramido)butyrate (hemihydrate) [CAS]	17097-76-6	EP	117260	Neurological	Attention deficit disorder
Calcium Iodobehenate		1319-91-1				
Calcium Iodostearate		1301-16-2				
Calcium Lactate		814-80-2				
Calcium Levulinate		591-64-0				
Calcium Ipasorbate		21065-60-9				
Calcium D-Carbamoylaspartate		16649-79-9				
calcium polycarbophil	Polycarbophil, calcium salt: [CAS]	126040-58-2			GI inflammatory/bowel disorders	Irritable bowel syndrome
Calcium Propionate		9003-97-8				
Calcium Succinate		4075-81-4				
		140-99-8				
caldaret	5-methyl-2-(1-piperazinyl)-benzenesulfonic acid monohydrate	133804-44-1			Cardiostimulant	Heart failure
Calusterone		17021-26-0				
Camazepam		36104-80-0				
camostat	Benzeneacetic acid, 4-[[4-[(aminoiminomethyl)amino]benzoyl]oxy]-, 2-(dimethylamino)-2-oxoethyl ester, monomethanesulfonate [CAS]	59721-28-7 59721-29-8 71079-09-9	US	4021472	GI inflammatory/bowel disorders	Pancreatitis
Camphor		76-22-2				
Camptothecin		4878-45-3				
camptothecin	4-Ethyl-4-hydroxy-1H-pyrano-[3'4':6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione					
Candesartan		139481-59-7			Formulation, optimized, microemulsion	Cancer, general
candesartan cilexetil	1H-Benzimidazole-7-carboxylic acid, 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, 1-[[(cyclohexyloxy)carbonyl]oxy]ethyl ester, (+/-)- [CAS]	145040-37-5	EP	520423	Antihypertensive, renin system	Hypertension, general
Candoxatril		123122-55-4				

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canertinib	N-[4-(3-Chloro-4-fluoro-phenylamino)-7-(3-morpholin-4-yl-propoxy)-quinazolin-6-yl]-acrylamide	289499-45-2			Anticancer, other	Cancer, lung, non-small cell
Canrenone		976-71-6				
Cantharidin		56-25-7				
cantuzumab mertansine	Maytansine, N2-deacetyl-N2-(3-mercapto-1-oxopropyl)-, conjugated humanized C242 monoclonal antibody	139504-50-0			Immunotoxin	Cancer, colorectal
capecitabine	Cytidine, 5-deoxy-5-fluoro-N-[(pentyloxy)carbonyl]- [CAS]	154361-50-9	EP	602454	Anticancer, antimetabolite	Cancer, breast
Capobenic Acid		21434-91-3				
capravirine	1H-Imidazole-2-methanol, 5-(3,5-dichlorophenyl)thio-4-(1-methylethyl)-1-(4-pyridinylmethyl carbamate (ester) [CAS]	178979-85-6			Antiviral, anti-HIV	Infection, HIV/AIDS
Capromab		1517763-64-3				
capsaicin cream	N-[(4-hydroxy-3-methoxyphenyl)methyl]-8-methyl-, (E)- [CAS]	404-86-4			Formulation, dermal, topical	Pain, post-herpetic
Captodiamine		486-17-9				
captopril	L-Proline, 1-(3-mercapto-2-methyl-1-oxopropyl)-, (S)- [CAS]	62571-86-2	US	4105776	Antihypertensive, renin system	Hypertension, general
captopril + HCTZ	L-Proline, 1-(3-mercapto-2-methyl-1-oxopropyl)-, (S)-, mixt. with 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide [CAS]	110075-07-5	US	4217347	Antihypertensive, renin system	
Capuride		5579-13-5				
carabersat	Benzamide, N-(6-acetyl-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl)-4-fluoro, (3R-trans)- [CAS]	184653-84-7	WO	9811890	Antiepileptic	Epilepsy, general
Caramiphen		77-22-5				
carazolol	2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[(1-methylethyl)amino]- [CAS]	57775-29-8	DE	2240589	Antihypertensive, adrenergic	
Carbachol		51-83-2				
carbamazepine	5H-Dibenz[b,f]azepine-5-carboxamide [CAS]	298-46-4			Formulation, modified-release, other	Epilepsy, general

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API Generic Name	API Chemical Name	CAS No.	Patent Reference	Example of Therapeutic Use	Example of Indication
Carbamide Peroxide		124-43-6			
Carbarsone		121-59-5			
Carbaryl		63-25-2			
Carbazochrome		13051-01-9 51460-26-5			
carbendazim	Methyl-2-benzimidazolecarbamate			Anticancer, other	Cancer, general
Carbenicillin		4697-36-3			
Carbeno:colone		5697-56-3			
Carbetapentane		77-23-6		Alimentary/Metabolic, other	Acidosis
Carbicarb	Carbonic acid disodium salt, mixt. with monosodium salt- [CAS]	72227-05-5			
Carbidopa	S-Alpha Hydrazino-3,4-dihydroxy-Alpha methyl benzene propanoic acid monohydrate +3-hydroxyL-tyrosine	28860-95-9		Formulation, fixed-dose combinations	Parkinson's disease
carbidopa+levodopa-1	.	22232-54-8			
Carbimazole		486-16-8			
Carbinoxamine		541-79-7			
Carbocisteine		13756-26-2			
Carbon Tetrachloride		638-23-3 56-23-5	EP 546272	Cystic fibrosis treatment	Cystic fibrosis
carboplatin	Platinum, diammine[1,1-cyclobutanedicarboxylato(2-)]-, (SP-4-2)- [CAS]	41575-94-4		Anticancer, alkylating	Cancer, ovarian
Carboprost		35700-23-3			
carboprost trometamol	Prosta-5,13-dien-1-oic acid, 9,11,15-trihydroxy-15-methyl-, (5Z,9 alpha.,11 alpha.,13E,15S)-, compd. with 2-amino-2-(hydroxymethyl)-1,3-propanediol(1:1) [CAS]	58551-69-2 74049-93-7	US 3728382	Prostaglandin	Abortion
Carboquone	2,5-Cyclohexadiene-1,4-dione, 2[2-[bis(2-chloroethyl)amino]-1-methoxyethyl]-3,6-bis(1-aziridinyl)-5-methyl- [CAS]	24279-91-2	DE 1905224	Anticancer, antibiotic	
Carbromal		77-65-6			

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Carbuterol		960-05-4				
Carbutamide		339-43-5				
Carbuterol		34866-47-2				
Carfimate		3567-38-2				
carglumic acid	N-Carbamoyl-L-glutamic acid	1188-38-1			Metabolic and enzyme disorders	Hyperammonaemia
Cargutocin		33605-67-3				
Carindacillin		35531-88-5				
cariporide	Benzamide, N-[aminoiminomethyl)-4-[(1-methylethyl)-3-(methylsulfonyl)- [CAS]	159138-80-4 159138-81-5	EP	589336	Antianginal	Angina, general
Cariporide		159138-80-4				
Carisoprodol		78-44-4				
carmofur	1(2H)-Pyrimidinecarboxamide, 5-fluoro-N-hexyl-3,4-dihydro-2,4-dioxo- [CAS]	61422-45-5	US	4071519	Anticancer, antimetabolite	
Carmoxirole		98323-83-2				
carmustine	Urea, N,N'-bis(2-chloroethyl)-N-nitroso- [CAS]	154-93-8			Formulation, Implant	Cancer, brain
Carnitine		461-06-3				
Caroverine		23465-76-1				
Caroxazone		19464-39-6				
Carphenazine		2622-30-2				
Carpipramine		5942-95-0				
carprofen	9H-Carbazole-2-acetic acid, 6-chloro-Alpha-methyl-, (+/-)- [CAS]	53716-49-7	US	3896145	Anti-inflammatory	
Carsalam		2037-95-8				
cartelol	2(1H)-Quinolinone, 5-[3-[(1,1-dimethylethyl)amino]-2-hydroxypropoxy]-3,4-dihydro-, monohydrochloride [CAS]	51781-06-7 51781-21-6	US	3910924	Antihypertensive, adrenergic	Glaucoma
Carticaine		23964-58-1				
Carubicin		50935-04-1				
Carumonam		87638-04-8				
Carvacrol		499-75-2				
carvedilol	2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-[CAS]	72956-09-3	EP	4920	Antihypertensive, adrenergic	Hypertension, general

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference	Example of Therapeutic Use	Example of Indication
Carvone		99-49-0			
Cascartillin		10118-56-6			
caspofungin	Pneumocandin B0, 1-[(4R,5S)-5-[(2-aminoethyl)amino]-N2-(10,12-dimethyl-1-oxotetradecyl)-4-hydroxy-L-ornithine]-5-(dihydro-3-hydroxy-L-ornithine), diacetate (salt) [CAS]	162808-62-0 179463-17-3	WO	9421677	Antifungal	Infection, Aspergillus
Catechin		154-23-4			
cathepsin K inhibitors	N-(1-benzothien-2-ylcarbonyl)-N-[2-(2-fluorophenyl)-4-oxo-1,2,3,4-tetrahydropyrimidin-5-yl]-L-leucinamide		WO	9613323	Osteoporosis treatment	Osteoporosis
cathepsin S inhibitors	N-(1-benzothien-2-ylcarbonyl)-N-[2-(2-fluorophenyl)-4-oxo-1,2,3,4-tetrahydropyrimidin-5-yl]-L-leucinamide				Antiasthma	Asthma
CC-401			US	6342595	Immunosuppressant	Arthritis, rheumatoid
CCI-779	Rapamycin 42-(3-hydroxy-2-(hydroxymethyl)-2-methylpropanoate) [CAS]	162635-04-3	WO	9730019	Anticancer, antibiotic	Cancer, renal
CCR5 antagonists			WO	9732019	Antiviral, anti-HIV	Infection, HIV/AIDS
CDC-394			US	6340601	Anticancer, other	Cancer, myeloma
CDC-801			US	5965614	GI inflammatory/bowel disorders	Crohn's disease
CEE-03-310	1H-3-Benzazepin-7-ol, 5-[2,3-dihydro-7-benzofuranyl)- 2,3,4,5-tetrahydro-3-methyl-4-nitro, (5S)- [CAS]	128022-68-4	EP	347672	Dependence treatment	Addiction, alcohol
cefaclor	5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[(aminophenylacetyl)amino]-3-chloro-8-oxo-, [6R-[6alpha,7(R*)]]- [CAS]	53994-73-3 70356-03-5	GB	1461323	Cephalosporin, oral	Infection, Haemophilus influenzae prophylaxis
cefadroxil	5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[(aminohydroxyphenylacetyl)amino]-3-methyl-8-oxo-, [6R-[6alpha,7(R*)]]- [CAS]	50370-12-2 66592-87-8	GB	1240687	Cephalosporin, oral	Infection, general
cefalexin	5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[aminophenylacetyl)amino]-3-methyl-8-oxo-, [CAS]	105879-42-3 15686-71-2	US	4775751	Cephalosporin, oral	Infection, respiratory tract, upper

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API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
cefalexin pivoxil	5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[(aminophenylacetyl)amino]-3-methyl-8-oxo-, (2,2-dimethyl-1-oxopropoxy)methyl ester, monohydrochloride, [6R-[6Alpha,7ß(R*)]]- [CAS]	27726-31-4			Cephalosporin, oral	Infection, general
cefamandole	7-D-mandelamido-3[[(1-methyl-1H-tetrazol-5-yl)thio]methyl]-3-cephem-4-carboxylic acid	34444-01-4	US	3641021	Cephalosporin, injectable	Infection, general
cefatrizine	5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[amino(4-hydroxyphenyl)acetyl]amino]-8-oxo-3-[(1H-1,2,3-triazol-4-ylthio)methyl]-, [6R-[6Alpha,7ß(R*)]]- [CAS]	51627-14-6	GB	1460914	Cephalosporin, oral	Infection, general
Cefazedone		56187-47-4				
Cefazolin		25953-19-9				
Cefbuperazone		76610-84-9				
cefcapene pivoxil	7ß-[(Z)-2-(2-amino-4-thiazolyl)-2-pentenoylamino]-3-carbamoyloxymethyl-3-cephem-4-carboxylic acid, pivaloyloxymethyl ester HCl- [CAS]	105889-45-0 105889-46-1	GB	2173194	Cephalosporin, oral	Infection, respiratory tract, general
Cefclidin		105239-91-6				
cefdinir	5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[(2-amino-4-thiazolyl)(hydroxyimino)acetyl]amino]-3-ethenyl-8-oxo-, [6R-[6Alpha,7ß(Z)]]- [CAS]	91832-40-5	EP	105459	Cephalosporin, oral	Infection, dermatological
cefditoren pivoxil	5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[(2-amino-4-thiazolyl)(methoxyimino)acetyl]amino]-3-[2-(4-methyl-5-thiazolyl)ethenyl]-8-oxo-, (2,2-dimethyl-1-oxopropoxy)methyl ester, [6R-[3(Z),6Alpha,7ß(Z)]]- [CAS]	104145-95-1 104146-53-4 117467-28-4	JP	61178991	Cephalosporin, oral	Infection, general

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API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
cefepime	Pyrrolidinium, 1-[[7-[[(2-amino-4-thiazolyl)(methoxyimino)acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1-methyl-, hydroxide, inner salt, [6R-[6Alpha,7Beta(Z)]]- [CAS]	107648-80-6 123171-59-5 88040-23-7	EP	531981	Cephalosporin, injectable	Infection, respiratory tract, lower
Cefetamet						
cefetamet pivoxil	5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[(2-amino-4-thiazolyl)(methoxyimino)acetyl]amino]-3-methyl-8-oxo-, (2,2-dimethyl-1-oxopropoxy)methyl ester, monohydrochloride, [6R-[6Alpha,7Beta(Z)]]- [CAS]	65052-63-3 111896-23-2	GB	1561854	Cephalosporin, oral	Infection, general
cefixime	5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[(2-amino-4-thiazolyl)[(carboxymethoxy)imino]acetyl]amino]-3-ethenyl-8-oxo-, [6R-[6Alpha,7Beta(Z)]]- [CAS]	79350-37-1	EP	30630	Cephalosporin, oral	Infection, general
cefmenoxime	5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[(2-amino-4-thiazolyl)(methoxyimino)acetyl]amino]-3-[[(1-methyl-1H-tetrazol-5-yl)thio]methyl]-8-oxo-, [6R-[6Alpha,7Beta(Z)]]- [CAS]	66085-01-0 75738-58-8	GB	1536281	Cephalosporin, injectable	Infection, ocular
cefmetazole	5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[[(cyanomethyl)thio]acetyl]amino]-7-methoxy-3-[[(1-methyl-1H-tetrazol-5-yl)thio]methyl]-8-oxo-, (6R-cis)- [CAS]	56796-20-4 56796-39-5	GB	1449420	Cephalosporin, injectable	Infection, general
cefminox	5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[[(2-amino-2-carboxyethyl)thio]acetyl]amino]-7-methoxy-3-[[(1-methyl-1H-tetrazol-5-yl)thio]methyl]-8-oxo-, [6R-[6Alpha,7Alpha,7(S*)]]- [CAS]	84305-41-9	EP	24879	Cephalosporin, injectable	Infection, urinary tract

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API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
cefodizime	5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[(2-amino-4-thiazolyl)(methoxyimino)acetyl]amino]-3-[[[5-(carboxymethyl)-4-methyl-2-thiazolyl]thio]methyl]-8-oxo-, [6R-[6Alpha,7&(Z)]]- [CAS]	69739-16-8 86329-79-5	US	4590267	Cephalosporin, injectable	Infection, respiratory tract, lower
cefonicid	5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[(hydroxyphenylacetyl)amino]-8-oxo-3-[[[1-(sulfomethyl)-1H-tetrazol-5-yl]thio]methyl]-, disodium salt, [6R-[6Alpha,7&(R*)]]- [CAS]	61270-78-8 61270-58-4	GB	1547473	Cephalosporin, injectable	Infection, general
cefoperazone	5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[[[(4-ethyl-2,3-dioxo-1-piperazinyl)carbonyl]amino](4-hydroxyphenyl)acetyl]amino]-3-[[(1-methyl-1H-tetrazol-5-yl)thio]methyl]-8-oxo-, [6R-[6Alpha,7&(R*)]]- [CAS]	62893-19-0	GB	1508071	Cephalosporin, injectable	Infection, general
cefoperazone + sulbactam		92739-15-6	US	4234579	Antibiotic, other	Infection, general
Ceforanide		60925-61-3				
cefoselis	5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[(2-amino-4-thiazolyl)(methoxyimino)acetyl]amino]-3-[[2,3-dihydro-2-(2-hydroxyethyl)-3-imino-1H-pyrazol-1-yl]methyl]-8-oxo-, [6R-[6Alpha,7&(Z)]]	122841-12-7 122841-10-5	EP	307804	Cephalosporin, injectable	Infection, general
cefotaxime	(6R,7R)-7-[[(2-amino-4-thiazolyl)(methoxyimino)acetyl]amino]cephalosporanic acidsodium salt	64485-93-4 63527-52-6	GB	1580621	Cephalosporin, injectable	Infection, general
Cefotetan		69712-56-7				
cefotiam	5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[(2-amino-4-thiazolyl)acetyl]amino]-3-[[[1-[2-(dimethylamino)ethyl]-1H-tetrazol-5-yl]thio]methyl]-8-oxo-, (6R-trans)- [CAS]	61622-34-2 66309-69-1	US	4080498	Cephalosporin, injectable	Infection, general

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cefoflam hexetil	1-(cyclohexyloxycarbonyloxy)ethyl 7[6-[2-(2-aminothiazol-4-yl)acetamido]-3-[[[1-[2-dimethylaminoethyl]-1H-tetrazol-5-yl]thio]methyl]cosph-3-em-4-carboxylate 2HCl [CAS]	95789-30-3	EP	1228029	Cephalosporin, oral	Infection, respiratory tract, lower
cefoxitin	5-Thia-1-azabicyclo(4.2.0)oct-2-ene-2-carboxylic acid, 3-((aminocarbonyl)oxy)methyl)-7-methoxy-8-oxo-7-(2-thienylacetyl)amino)-, monosodium salt, (6R-cis)- [CAS]	33564-30-6 35607-66-0	GB	1348884	Cephalosporin, oral	Infection, general
cefozopran	Imidazo[1,2-b]pyridazinium, 1-[[7-[[(5-amino-1,2,4-thiadiazol-3-yl)(methoxyimino)acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-, hydroxide, inner salt, [6R-[6Alpha,7b(Z)]]- [CAS]	113359-04-9	EP	203271	Cephalosporin, injectable	Infection, general
cefpimizole	Pyridinium, 1-[[2-carboxy-7-[[[(5-carboxy-1H-imidazol-4-yl)carbonyl]amino]phenylacetyl]amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-4-(2-sulfoethyl)-, hydroxide, inner salt, [6R-[6Alpha,7b(R*)]]- [CAS]	84880-03-5 85287-61-2	EP	60028	Cephalosporin, injectable	Infection, respiratory tract, general
cefpiramide	5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[[[4-hydroxy-6-methyl-3-pyridinyl]carbonyl]amino](4-hydroxyphenyl)acetyl]amino]-3-[[(1-methyl-1H-tetrazol-5-yl)thio]methyl]-8-oxo-, [6R-[6Alpha,7b(R*)]]- [CAS]	70797-11-4	US	4156724	Cephalosporin, injectable	Infection, general
cefpirome	5H-1,4-Pyridinium, 1-[[7-[[(2-amino-4-thiazolyl)(methoxyimino)acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-6,7-dihydro-, hydroxide, inner salt, [6R-[6Alpha,7b(Z)]]- [CAS]	84957-29-9 98753-16-4 87239-81-4	EP	84740	Cephalosporin, injectable	Infection, respiratory tract, lower
Cefpodoxime Proxetil						

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API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
cefprozil	5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[(amino(4-hydroxyphenyl)acetyl)amino]-8-oxo-3-(1-propenyl)-, [6R-[6Alpha,7Beta(R*)]]- [CAS]	92665-29-7 121123-17-9	GB	2173798	Cephalosporin, oral	Infection, dermatological
cefroxadine	5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[(amino-1,4-cyclohexadien-1-yl)acetyl)amino]-3-methoxy-8-oxo-, [6R-[6Alpha,7Beta(R*)]]- [CAS]	51762-05-1	GB	1435111	Cephalosporin, oral	Infection, general
cefsulodin	Pyridinium, 4-(aminocarbonyl)-1-[[2-carboxy-8-oxo-7-[(phenylsulfoacetyl)amino]-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-, hydroxide, inner salt, [6R-[6Alpha,7Beta(R*)]]- [CAS]	52152-93-9 62567-73-9	GB	1387656	Cephalosporin, injectable	Infection, pseudomonal
ceftazidime	Pyridinium, 1-[[7-[[(2-amino-4-thiazolyl)[(1-carboxy-1-methylethoxy)imino]acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-, hydroxide, inner salt, [6R-[6Alpha,7Beta(Z)]]- [CAS]	72558-82-8	GB	2025398	Cephalosporin, injectable	Infection, respiratory tract, upper
Cefteram	-	82547-56-8				
Ceftezole	-	26973-24-0				
ceftibuten	5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[2-(2-amino-4-thiazolyl)-4-carboxy-1-oxo-2-butenyl]amino]-8-oxo-, [6R-[6Alpha,7Beta(Z)]]- [CAS]	97519-39-6	EP	136721	Cephalosporin, oral	Infection, respiratory tract, lower
ceftizoxime	5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[(2-amino-4-thiazolyl)(methoxyimino)acetyl]amino]-8-oxo-, [6R-[6Alpha,7Beta(Z)]]- [CAS]	68401-81-0 68401-82-1	GB	1600735	Cephalosporin, injectable	Infection, general

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API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
ceftizoxime alapivoxil	5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[[2-[(2-amino-1-oxopropyl)amino]-4-thiazolyl](methoxyimino)acetyl]amino]-8-oxo-, (2,2-dimethyl-1-oxopropoxy)methyl ester, monohydrochloride, [6R-[6Alpha,7ß(Z(S*))]]- [CAS]	113812-94-5 135767-36-1	JP	62209112	Cephalosporin, oral	Infection, general
ceftriaxone	5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[(2-amino-4-thiazolyl)(methoxyimino)acetyl]amino]-8-oxo-3-[[(1,2,5,6-tetrahydro-2-methyl-5,6-dioxo-1,2,4-triazin-3-yl)thio]methyl]-, [6R-[6Alpha,7ß(Z)]]- [CAS]	73384-59-5 74578-69-1	GB	2022090	Cephalosporin, injectable	Infection, respiratory tract, lower
cefuroxime axetil	5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 3-[[(aminocarbonyl)oxy]methyl]-7-[[2-furanyl(methoxyimino)acetyl]amino]-8-oxo-, 1-(acetyloxy)ethyl ester, [6R-[6Alpha,7ß(Z)]]- [CAS]	15686-71-2 64544-07-6	GB	1571683	Cephalosporin, oral	Infection, respiratory tract, upper
cefuroxime	5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 3-[[(aminocarbonyl)oxy]methyl]-7-[[2-furanyl(methoxyimino)acetyl]amino]-8-oxo-, [6R-[6Alpha,7ß(Z)]]- [CAS]	55268-75-2 56238-63-2	GB	1453049	Cephalosporin, injectable	Infection, general
Cefuzonam		82219-78-1				
celecoxib	Benzenesulfonamide, 4-(5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)- [CAS]	169590-42-5	US	5760068	Antiarthritic, other	Arthritis, rheumatoid
celgosivir	Butanoic acid, octahydro-1,7,8-trihydroxy-6-indolizinyl ester, [1S-(1Alpha,6ß,7Alpha,8ß,8aß)]- [CAS]	121104-96-9	US	5017563	Antiviral, other	Infection, hepatitis virus, general
celiprolol	Urea, N'-[3-acetyl-4-[3-[(1,1-dimethylethyl)amino]-2-hydroxypropoxy]phenyl]-N,N-diethyl- [CAS]	56980-93-9 57470-78-7	GB	1441359	Antihypertensive, adrenergic	Angina, unstable
Cellulose Ethyl Hydroxyethyl Ether		9004-58-4				

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API Generic Name	API Chemical Name	CAS No.	Patent Reference	Example of Therapeutic Use	Example of Indication
Centchroman		31477-60-8			
CEP-1347	9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5, 16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- [CAS]	156177-65-0	WO 9731002	Antiparkinsonian	Parkinson's disease
CEP-701	9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocin-1-one, 2,3,9,10,11,12-hexahydro-10-hydroxy-10-(hydroxymethyl)-9-methyl-, (9S,10S,12R)- [CAS]	111358-88-4		Anticancer, antimetabolite	Cancer, prostate
Cephacetrile		23239-41-0			
Cephaeline		483-17-0			
Cephalexin		15686-71-2			
Cephaloglycin		3577-1-3			
Cephaloridine		50-59-9			
Cephalosporin C		61-24-5			
Cephalothin		153-61-7			
Cephapirin		24356-60-3			
Cephradine		38821-53-3			
Cerivastatin		145599-86-6			
Ceronapril		111223-26-8			
certoparin	Heparin [CAS]	9005-49-6		Anticoagulant	Thrombosis, venous
Ceruletide		17650-98-5			
Cervíprost	Prosta-5,13-dien-1-oic acid, 11,15-dihydroxy-9-oxo-, (5Z,11Alpha,13E,-15S)- [CAS]	363-24-6		Formulation, dermal, topical	
Cetalkonium		122-18-9			
Cetamolol		34919-98-7			
Cethexonium		1794-74-7			

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API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
cethromycin	2H-Oxacyclotetradecino[4,3-d]oxazole-2,6,8,14(1H,7H,9H)-tetrone 4-ethyloctahydro-3a,7,9,11,13,15-hexamethyl-11-[(3-(3-quinolinyl)-2-propenyl)oxy]-10-((3,4,6-trideoxy-3-(dimethylamino)-ß-D-xylo-hexapyranosyl)oxy)-,(3a S,4R,7R,9R,10R,11R,13R,15R,15aR)-[CAS]	205110-48-1	EP	929563	Macrolide antibiotic	Infection, respiratory tract, general
Cetiedil		14176-10-4				
Cetirizine		83881-51-0				
cetirizine	Acetic acid, [2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-, [CAS]	83881-51-0 83881-52-1	EP	58146	Antiallergic, non-asthma	Allergy, general
cetirizine+pseudoephedrine	Acetic acid, [2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-, dihyrochloride, Benzenemethanol, Alpha-[1-(methylamino)ethyl]-, hydrochloride, [S-(R*R*)]-	83881-52-1 90-82-4			Formulation, optimized, microencapsulate	Allergy, general
Cetotiamine		137-76-8				
Cetoxime		25394-78-9				
cetraxate	Benzenepropanoic acid, 4-[[[4-(aminomethyl)cyclohexyl]carbonyl]oxy]-, trans-[CAS]	27724-96-5 34675-84-8	JP	48075547	Antiulcer	
Cetrimonium		57-09-0				
Cetrorelix		120287-85-6				
Cetyldimethylethylammonium		124-03-8				
Cetylpyridinium		123-03-5				
cevimeline	Spiro[1-azabicyclo[2.2.2]octane-3,5'-[1,3]oxathiolane], 2'-methyl-, cis- [CAS]	107220-27-9 107233-08-9	EP	205247	Stomatological	Sjogren's syndrome
CG-1521	7-phenyl-2,4,6-heptatrienoylhydroxamic acid				Anticancer, other	Cancer, general
Chaulmoogric Acid		29106-32-9				
Chenodiol		474-25-9				

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API Generic Name	API Chemical Name	CAS No.	Patent Reference	Example of Therapeutic Use	Example of Indication
ChF-3361			EP 951466	Analgesic, other	Pain, neuropathic
Chlophedianol		791-35-5			
Chlorcaldrine		800-22-6			
chloral	1,1-Ethanediol, 2,2,2-trichloro- [CAS]	302-17-0 2218-68-0 515-82-2		Formulation, transmucosal, systemic	Insomnia
Chlorambucil		305-03-3			
Chloramine-B		127-52-6			
Chloramine-T		127-65-1			
Chloraminophenamide		121-30-2			
Chloramphenicol		56-75-7			
Chlorazanil		500-42-5			
Chlorbenzoxamine		522-18-9			
Chlorbetamide		97-27-8			
Chlorcyclizine		82-93-9			
Chlordantoin		5588-20-5			
Chlordiazepoxide		58-25-3			
Chlorguanide		500-92-5			
Chlorhexadol		3563-58-4			
chlorhexidine	2,4,11,13-Tetraazatetradecanediimidamide, N,N''-bis(4-chlorophenyl)-3,12-dimino- [CAS]	55-56-1		Formulation, other	Xerostomia, Periodontitis
Chlorisondamine		69-27-2			
Chlormadinone		302-22-7			
Chlormerodrin		62-37-3			
Chlormezanone		80-77-3			
Chlormidazole		3689-76-7			
Chlornaphazine		494-03-1			
Chlorogazodin		502-98-7			
Chlorophyll		1406-65-1			
Chloroprednisone		52080-57-6			
Chloroprocaine		3858-89-7			
Chloropyramine		59-32-5			

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API Generic Name	API Chemical Name	CAS No.	Patent Reference	Example of Therapeutic Use	Example of Indication
Chloroquine		54-05-7			
Chlorothen		148-65-2			
Chlorothiazide		58-94-6			
Chlorotrianisene		569-57-3			
Chloroxine		773-76-2			
Chloroxylenol		88-04-0			
Chlorozotocin		54749-90-5			
chlorphenamine	2-Pyridinepropanamine, Gamma-(4-chlorophenyl)-N,N-dimethyl- [CAS]	132-22-9		Formulation, modified-release, other	Allergy, general
Chlorphenesin		104-29-0			
		886-74-8			
Chlorpheniramine		132-22-9			
Chlorphenoxamide		3576-64-5			
Chlorphenoxamine		77-38-3			
Chlorphentermine		461-78-9			
Chlorproethazine		84-01-5			
Chlorproguanil		537-21-3			
chlorproguanil + dapsone	4,4'-Sulfonyldianiline + 1-(3,4-Dichlorophenyl)-5-isopropylbiguanide	537-21-3 80-08-0		Antimalarial	Infection, malaria
Chlorprothixene		50-53-3			
Chlorpropamide		94-20-2			
Chlorprothixene		113-59-7			
Chlorquinaldol		72-80-0			
Chlortetracycline		57-62-5			
Chlorthalidone		77-36-1			
Chlorthenoxazin(e)		132-89-8			
Chlorzoxazone		95-25-0			
Cholic Acid		81-25-4			
Choline		67-48-1 2016-36-6 28319-77-9			

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API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
choline theophyllinate	Ethanaminium, 2-hydroxy-N,N,N-trimethyl-, salt with 3,7-dihydro-1,3-dimethyl-1H-purine-2,6-dione (1:1) [CAS]	4499-40-5			Formulation, modified-release, other	
choline-L-alfoscerate	Ethanaminium, 2-[[(2,3-dihydroxypropoxy)hydroxyphosphinyl]oxy]-N,N,N-trimethyl-, hydroxide, inner salt, (R)- [CAS]	28319-77-9	JP	55028955	Cognition enhancer	Amnesia
Chromocarb		4940-39-0				
Chromonar		804-10-4				
Chrysoidine		532-82-1				
CHS-828	Guanidine, N-[6-(4-chlorophenoxy)hexyl]-N'-cyano-N''-4-pyridinyl- [CAS]	200484-11-3	US	5696140	Anticancer, other	Cancer, general
CI-1031	Glycine, N-[2-[5-(aminoiminomethyl)-2-hydroxyphenoxy]-6-[3-(4,5-dihydro-1-methyl-1H-imidazol-2-yl)phenoxy]-3,5-difluoro-4-pyridinyl]-N-methyl- [CAS]	183305-24-0	WO	9638421	Antianginal	Angina, unstable
CI-1040	Benzamide, 2-[(2-chloro-4-iodophenyl)amino]-N-(cyclopropylmethoxy)-3,4-difluoro- [CAS]	212631-79-3	WO	9837881	Anticancer, other	Cancer, general
cibenzoline	1H-Imidazole, 2-(2,2-diphenylcyclopropyl)-4,5-dihydro- [CAS]	53267-01-9	GB	1417174	Antiarrhythmic	Arrhythmia, general
ciclesonide	Pregna-1,4-diene-3,20-dione 16,17-((cyclohexylmethylene)bis(oxy))-11-hydroxy-21-(2-methyl-1-oxopropoxy) (11ß,16Alpha) [CAS]	126544-47-6	DE	4129535	Antiasthma	Asthma
cicletanine	Furo[3,4-c]pyridin-7-ol, 3-(4-chlorophenyl)-1,3-dihydro-6-methyl-, (+/-)- [CAS]	82747-56-6 89943-82-8	US	4383998	Antihypertensive, other	
ciclonicate	3-Pyridinecarboxylic acid, 3,3,5-trimethylcyclohexyl ester, trans- [CAS]	53449-58-4	DE	1910481	Vasodilator, peripheral	Cancer, lung, small cell
ciclopirox	2(1H)-Pyridinone, 6-cyclohexyl-1-hydroxy-4-methyl-, [CAS]	41621-49-2 29342-05-0	US	3883545	Antifungal	Infection, fungal, general
Ciclosidomine		66564-16-7				

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API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
ciclosporin A	Cyclosporin A- [CAS]	59865-13-3			Formulation, optimized, microemulsion	Transplant rejection, general
cidofovir	Phosphonic acid, [[2-(4-amino-2-oxo-1(2H)-pyrimidinyl)-1-(hydroxymethyl)ethoxy]methyl]-, (S)- [CAS]	113852-37-2	EP	253412	Antivirals, other	Infection, cytomegalovirus
Cifenline		53267-01-9				
cilansetron	4H-Pyrido[3,2,1-jk]carbazol-11(8H)-one, 5,6,9,10-tetrahydro-10-[(2-methyl-1H-imidazol-1-yl)methyl]-, (R)- [CAS]	120635-74-7	EP	297651	GI inflammatory/bowel disorders	Irritable bowel syndrome
Cilastatin		82009-34-5				
cilazapril	6H-Pyridazino[1,2-a][1,2]diazepine-1-carboxylic acid, 9-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]octahydro-10-oxo-, [1S-[1R(R*),9R*]]- [CAS]	88768-40-5 90139-06-3	GB	2126994	Antihypertensive, renin system	Hypertension, general
cilengitide	Cyclo[L-arginylglycyl-L-alpha-aspartyl-D-phenylalanyl-N-methyl-L-valyl] [CAS]	188968-51-6	EP	770622	Anticancer, other	Cancer, lung, non-small cell
cilnidipine	3,5-Pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-[3-nitrophenyl]-, 2-methoxyethyl 3-phenyl-2-propenyl ester- [CAS]	102106-21-8 132203-70-4	EP	161877	Antihypertensive, other	Hypertension, general
cilomilast	Cis-4-cyano-4-[3-cyclopentyloxy]-4-methoxyphenyl]cyclohexane-1-carboxylic acid	153259-65-5	US	5602167	COPD treatment	Chronic obstructive pulmonary disease
cilostazol	2(1H)-Quinolinone, 6-[4-(1-cyclohexyl-1H-tetrazol-5-yl)butoxy]-3,4-dihydro- [CAS]	73963-72-1	GB	2033893	Antithrombotic	Peripheral vascular disease
Cimetidine		51481-61-9				
cimetropium	3-Oxa-9-azoniatricyclo[3.3.1.02,4]nonane, 9-(cyclopropylmethyl)-7-[3-hydroxy-1-oxo-2-phenylpropoxy]-9-methyl-, (7S)-(1.Alpha.,2.bet.,4.bet.,5.Alpha.,7S)]- [CAS]	51598-60-8	US	3853886	Antispasmodic	Muscle spasm, general
cinacalcet	1-naphthalenemethanamine, Alpha-methyl-N-[3-[3-(trifluoromethyl)phenyl]propyl]-, (AlphaR)-,	364782-34-3			Hormone	Hyperparathyroidism

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API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Cinchonidine		485-71-2				
Cinchonine		118-10-5				
Cinchophen		132-60-5				
Cinepazet		23887-41-4				
Cinepazide		23887-46-9				
cinepazide	Piperazine, 1-[2-oxo-2-(1 pyrrolidinyl)ethyl]-4-[1-oxo-3-(3,4,5-trimethoxyphenyl)-2-propenyl]-, (Z)-2-butenedioate (1:1) [CAS]	26328-04-1	GB	1218591	Vasodilator, peripheral	Peripheral vascular disease
Cinitapride		66564-14-5				
Cinmetacin		20168-99-4				
Cinnamedrine		90-66-8				
Cinnarizine		298-57-7				
cinolazepam	1H-1,4-Benzodiazepine-1-propanenitrile, 7-chloro-5-(2-fluorophenyl)-2,3-dihydro-3-hydroxy-2-oxo- [CAS]	75696-02-5	DE	2950235	Hypnotic/Sedative	Insomnia
cinoxacin	[1,3]Dioxolo[4,5-g]cinnoline-3-carboxylic acid, 1-ethyl-1,4-dihydro-4-oxo- [CAS]	28657-80-9	GB	1296753	Quinolone antibacterial	Infection, urinary tract
Cinoxate		104-28-9				
Cinromide		58473-74-8				
Cioteronel		89672-11-7				
cipamfylline	1H-Purine-2,6-dione, 8-amino-1,3-bis(cyclopropylmethyl)-3,7-dihydro- [CAS]	132210-43-6	EP	382282	Antipruritic/Inflamm, allergic	Eczema, atopic
cipralisant	1H-Imidazole, 4-[(1R,2R)-2-(6,6-dimethyl-1-hexynyl)cyclopropyl]- [CAS]	213027-19-1	US	6008240	Psychostimulant	Attention deficit disorder
ciprofibrate	Propanoic acid, 2-[4-(2,2-dichlorocyclopropyl)phenoxy]-2-methyl- [CAS]	52214-84-3	GB	1386828	Hypolipaemic/Antiatherosclerosis	Hyperlipidaemia, general
ciprofloxacin	3-Quinolinecarboxylic acid, 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)- [CAS]	85721-33-1	US	4670444	Quinolone antibacterial	Infection, general

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ciprofloxacin-fluocinolone,SAL	3-Quinolinecarboxylic acid, 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-+ (6Alpha, 16, 16Alpha)-6,9-Difluoro-11,21-dihydroxy-16,17-[(1-methylethylidene)bis(oxy)]-pregna-1,4-diene-3,20-dione	63269-31-8		Formulation, fixed-dose combinations	Otitis
Ciramadol					
cisapride	Benzamide, 4-amino-5-chloro-N-[1-[3-(4-fluorophenoxy)propyl]-3-methoxy-4-piperidinyl]-2-methoxy-, cis- [CAS]	81098-60-4	EP 76530	Gastroprokinetic	
cisatracurium	Isoquinolinium, 2,2'-[1,5-pentanediylbis(oxy)3-oxo-3,1-propanediyl)]bis[1-[(3,4-dimethoxyphenyl)methyl]]-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-, [1R-[1Alpha,2Alpha(1'R*,2'R*)]]-, [CAS]	96946-42-8	US 5453510	Muscle relaxant	Surgery adjunct
cisplatin	Platinum, diamminedichloro-, (SP-4-2)- [CAS]	15663-27-1	US 4177263	Anticancer, alkylating	
citalopram	5-Isobenzofurancarbonitrile, 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro- [CAS]	59729-32-7 59729-33-8	GB 1526331	Antidepressant	Depression, general
citicoline	Cytidine 5'-(trihydrogen diphosphate), P'-[2-(trimethylammonio)ethyl]ester, hydroxide, inner salt [CAS]	987-78-0	JP 39006541	Cognition enhancer	Infarction, cerebral
Citiolone		1195-16-0			
Citric Acid		77-92-9			
Citrulline		372-75-8			
cizolirtine	Ethanamine, N,N-dimethyl-2-[(1-methyl-1H-pyrazol-5-yl)phenylmethoxy]-, 2-hydroxy-1,2,3-propanetricarboxylate [CAS]	142155-44-0		Urological	Incontinence
CJ-13610	4-(3-(4-(2-Methyl-imidazol-1-yl)-phenylsulfamyl)-phenyl)-tetrahydro-pyran-4-carboxylic acid amide			COPD treatment	Chronic obstructive pulmonary disease

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CKD-602	1H-Pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione, 4-ethyl-4-hydroxy-11-[2-[(1-methylethyl)amino]ethyl]-, monohydrochloride, (4S)- [CAS]	213819-48-8	WO	9902530	Anticancer, other	Cancer, ovarian
cladribine	Adenosine, 2-chloro-2'-deoxy- [CAS]	4291-63-8	EP	173069	Anticancer, antimetabolite	Cancer, leukaemia, hairy cell
Clanobutin		30544-61-7				
clarithromycin	Erythromycin, 6-O-methyl- [CAS]	81103-11-9	EP	41355	Macrolide antibiotic	Infection, respiratory tract, lower
Clavulanate, Disodium						
Clavulanic Acid		58001-44-8				
Clebopride		55905-53-8				
Clemastine		15686-51-8				
Clemizole		442-52-4				
Clenbuterol		37148-27-9				
Clentiazem		96125-53-0				
clevidipine	3,5-Pyridinedicarboxylic acid, 4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-, methyl (1-oxobutoxy)methyl ester (±) [CAS]	167221-71-8	WO	9512578	Antihypertensive, other	Hypertension, general
clevudine	2,4(1H,3H)-Pyrimidinedione, 1-(2-deoxy-2-fluoro-b-L-arabinofuranosyl)-5-methyl- [CAS]	163252-36-6			Antiviral, other	Infection, hepatitis-B virus
Clidanac		28968-07-2				
Clidinium		3485-62-9				
Clinafloxacin		105956-97-6				
Clindamycin		18323-44-9				
clindamycin + tretinoin	L-threo-Alpha-D-galacto-Octopyranoside, methyl 7-chloro-6,7,8-trideoxy-6-[[[1-methyl-4-propyl-2-pyrrolidinyl]carbonyl]amino]-1-thio-, (2S-trans)- + retinoic acid				Formulation, fixed-dose combinations	Acne

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clindamycin	L-Threo-Alpha-D-galacto-octopyranoside, methyl 7-chloro-6,7,8-trideoxy-6-[[(1-methyl-4-propyl-2-pyrrolidinyl)carbonyl]amino]-1-thio-, 2-(dihydrogen phosphate), (2S-trans)-	18323-44-9 24729-96-2		Formulation, parenteral, other	Infection, gynaecological
Clinofibrate		30299-08-2			
Clinprost		88931-51-5			
clobazam	1H-1,5-Benzodiazepine-2,4(3H,5H)-dione, 7-chloro-1-methyl-5-phenyl- [CAS]	22316-47-8	GB 1214662	Anxiolytic	
Clobenfurol		3611-72-1			
Clobenoside		29899-95-4			
Clobenzepam		1159-93-9			
Clobenzorex		13364-32-4			
Clobenztropine		5627-46-3			
clobetasol	Pregna-1,4-diene-3,20-dione, 21-chloro-9-fluoro-11,17-dihydroxy-16-methyl-, (11S,16S)- [CAS]	25122-41-2		Formulation, dermal, topical	Psoriasis
clobetasone	Pregna-1,4-diene-3,11,20-trione, 21-chloro-9-fluoro-16-methyl-17-[1-oxobutoxy]-, (16S)- [CAS]	25122-57-0 54063-32-0	GB 1253831	Antipruritic/inflamm, allergic	
Clobutinol		14860-49-2			
Clocapramine		47739-98-0			
Clociclizine		296-55-5			
Cloconazole		77175-51-0			
Clocortolone		4828-27-7			
clodronate	Phosphonic acid, (dichloromethylene)bis- [CAS]	22560-50-5		Osteoporosis treatment, Anticancer, hormonal	Pain, cancer, Hypercalcaemia of malignancy
Clodronic Acid		10596-23-3			
clofarabine	2-chloro-9-(2-deoxy-2-fluoro-b-D-arabinofuranosyl)adenine			Anticancer, antimetabolite	Cancer, leukaemia, chronic lymphocytic

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clofazimine	3-(p-chloroanilo)-10-(p-chlorophenyl)-2,10-dihydro-2-(isopropylimino)-phenazine	2030-63-9			Formulation, optimized, microencapsulate	Infection, tuberculosis
Clofenamide		671-95-4				
Clofibrate		637-07-0				
Clofibric Acid		882-09-7				
Cloflucarban		369-77-7				
Clofoctol		37693-01-9				
Cloforex		14261-75-7				
Clomacran		5310-55-4				
Clomestrone		4091-76-2				
Clometacin		25803-14-9				
Clomethiazole		533-45-9				
Clometocillin		1926-49-4				
Clomiphene		303-49-1				
Clomipramine		911-45-6				
Clomocycline		1181-54-0				
clonazepam	2H-1, 4-Benzodiazepin-2-one, 5-(2-chlorophenyl)-1,3-dihydro-7-nitro- [CAS]	1622-61-3	US	4316897	Antiepileptic	Epilepsy, general
clonidine	1H-Imidazol-2-amine, N-(2,6-dichlorophenyl)-4,5-dihydro- [CAS]	4205-90-7	US	4060084	Formulation, transdermal, patch	Hypertension, general
Clonitazene		3861-76-5				
Clonitrate		2612-33-1				
Clonixin		17737-65-4				
Clopamide		636-54-4				
Clopenthixol		982-24-1				
Cloperastine		3703-76-2				
clopidogrel	Thieno[3,2-c]pyridine-5(4H)-acetic acid, Alpha-(2-chlorophenyl)-6,7-dihydro-, methyl ester, (S)- [CAS]	120202-48-4 90055-48-4 113665-84-2	EP	99802	Antithrombotic	Infarction, myocardial
Clopirac		42779-82-8				
Cloprednol		5251-34-3				
cloranolol	2-Propanol, 1-(2,5-dichlorophenoxy)-3-[(1,1-dimethylethyl)amino]- [CAS]	39563-28-5 54247-25-5	US	4310549	Antihypertensive, adrenergic	

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API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Clorazepic Acid		23887-31-2				
Clorexolone		2127-1-7				
cloricromene	Acetic acid, [[8-chloro-3-[2-(diethylamino)ethyl]-4-methyl-2-oxo-2H-1-benzopyran-7-yl]oxy]-, ethyl ester [CAS]	68206-94-0	US	4349566	Vasodilator, coronary	Peripheral vascular disease
Clorindione		1146-99-2				
Clorprenaline		3811-25-4				
Clortermine		10389-73-8				
Clospirazine		24527-27-3				
Clostebol		1093-58-9				
Clothiapine		2058-52-8				
clotiazepam	2H-Thieno[2,3-e]-1,4-diazepin-2-one, 5-(2-chlorophenyl)-7-ethyl-1,3-dihydro-1-methyl- [CAS]	33671-46-4	US	3849405	Anxiolytic	Anxiety, general
clotrimazole	1-[(2-chlorophenyl)diphenylmethyl]-1H-imidazole	23593-75-1	US	3705172	Antifungal	
clotrimazole + betamethasone	Pregna-1,4-diene-3,20-dione, 9-fluoro-11-hydroxy-16-methyl-17,21-bis(1-oxopropoxy)-, (11ß,16ß)-, mixt. with 1-[(2-chlorophenyl)diphenylmethyl]-1H-imidazole [CAS]	92522-91-3			Formulation, fixed-dose combinations	Infection, fungal, general
Cloxacillin		61-72-3				
cloxazolam	Oxazolo[3,2-d][1,4]benzodiazepin-6(5H)-one, 10-chloro-11b-(2-chlorophenyl)-2,3,7,11b-tetrahydro- [CAS]	24166-13-0	US	3772371	Anxiolytic	
Cloxotestosterone		53608-96-1				
Cloxyquin		130-16-5				
clozapine	5H-Dibenzo[b,e][1,4]diazepine, 8-chloro-11-(4-methyl-1-piperazinyl)- [CAS]	5786-21-0	US	3539573	Neuroleptic	Schizophrenia
CMI-392	Trans-2-[3-methoxy-4-(2-p-chlorophenylthio)ethoxy-5-(N'-methyl-N'-hydroxyureidyl)methylphenyl]-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran	193739-23-0	US	5648486	Antipsoriasis	Psoriasis

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CMT-3	2-Naphthacenecarboxamide, 1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-, (4aS,5aR,12aS)- [CAS]	15866-90-7	US	5837696	Anticancer, other	Cancer, sarcoma, Kaposi's
CNI-1493	Decanediamide, N,N'-bis[3,5-bis[1-[(aminoiminomethyl)hydrazono]ethyl]phenyl]-, tetrahydrochloride [CAS]	164301-51-3	US	5750573	Anti-inflammatory	Psoriasis
CNS-5161	N'-[2-chloro-5-(methylthio)phenyl]-N-methyl-N-[3-(methylthio)phenyl]guanidine [CAS]	160754-76-7	WO	9427591	Analgesic, other	Pain, neuropathic
Cobamamide		13870-90-1				
Cocaethylene		529-38-4				
Cocaine		50-36-2				
Codeine		76-57-3 52-28-8				
CoFactor	5,10 methylene - tetrahydrofolate				Anticancer, antimetabolite	Cancer, colorectal
Colchicine		64-86-8				
colesevelam	1-Hexanaminium, N,N,N-trimethyl-6-(2-propenylamino)-, polymer with (chloromethyl)oxirane, 2-propen-1-amine and N-2-propenyl-1-decanamine, hydrochloride [CAS]	182815-44-7	US	5607669	Hypolipaemic/Antiatherosclerosis	Hyperlipidaemia, general
colestilan	1H-Imidazole, 2-methyl-, polymer with (chloromethyl)oxirane [CAS]	95522-45-5	JP	59155421	Hypolipaemic/Antiatherosclerosis	Hypercholesterolaemia
Colestipol		26658-42-4				
colforsin daropate	6-(3-dimethylaminopropionyl)forskolin-[CAS]	138605-00-2	EP	222413	Cardiostimulant	Heart failure
colfosceril	3,5,9-Trioxa-4-phosphapentacosan-1-aminium, 4-hydroxy-N,N,N-trimethyl-10-oxo-7-[(1-oxohexadecyl)oxy]-, hydroxide, inner salt, 4-oxide, (R)- [CAS]	63-89-8 99732-49-7	US	4826821	Lung Surfactant	Respiratory distress syndrome, infant
Collagraft		138331-02-9			Formulation, implant	Regeneration, bone
Colocynthin		1398-78-3				
Colpormon		1247-71-8				

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coluracetam	1-Pyrrolidineacetamide, 2-oxo-N-(5,6,7,8-tetrahydro-2,3-dimethylfuro[2,3-b]quinolin-4-yl)- [CAS]	135463-81-9	EP	427636	Cognition enhancer	Alzheimer's disease
combretastatin A-4 prodrug	disodium combretastatin-A-4-3-O-phosphate				Anticancer, other	Cancer, thyroid
compound B, Pharmacor			US	6362165	Antiviral, anti-HIV	Infection, HIV/AIDS
conivaptan	[1,1'-Biphenyl]-2-carboxamide, N-[4-[(4,5-dihydro-2-methylimidazo[4,5-d][1-benzazepin-6(1H)-yl)carbonyl]phenyl]-, [CAS]	168626-94-6	WO	9503305	GI inflammatory/bowel disorders	Hyponatreamia
Connettivina	Hyaluronic acid [CAS]	9004-61-9			Vulnerary	
Convallatoxin		508-75-8				
Coparaffinate		8001-80-3				
Corticocelin Ovine Triflucate						
Corticosterone		50-22-6				
Cortisone		53-06-5				
Cortivazol		1110-40-3				
Cosyntropin		16960-16-0				
Cotarnine		82-54-2				
Cotinine		486-56-6				
co-trimazine	Benzenesulfonamide, 4-amino-N-(2-pyrimidinyl)-, mixt. with 5-[(3,4,5-trimethoxyphenyl)methyl]-2,4-pyrimidinediamine [CAS]	39474-58-3			Trimethoprim and analogues	Infection, urinary tract
Coumetarol		4366-18-1				
CP-248	1H-Indene-3-acetamide, 5-fluoro-2-methyl-N-(phenylmethyl)-1-[(3,4,5-trimethoxyphenyl)methylene]-, (1Z)- [CAS]	200803-37-8	WO	9747303	Anticancer, other	Barrett's oesophagus
CP-461			US	5948779	Anticancer, other	Cancer, prostate
CPC-211	Acetic acid, dichloro-, sodium salt [CAS]	2156-56-1			Neuroprotective	Acidosis, lactic
CPI-1189	CPI 1189 [CAS]	210475-67-5	WO	9631462	Cognition enhancer	Dementia, AIDS-related
CRA-0450			WO	0202549	Anxiolytic	Unspecified

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
	Guanidine, N-methyl-N-[2-(phosphonooxy)ethyl]- [CAS]	6903-79-3			Antifungal	
creatinol-O-phosphate	Oxirane, methyl-, polymer with oxirane, block [CAS]	106392-12-5	US	4837014	Antisickling	Anaemia, sickle cell
crobenetine	(2R,6S)-3-[2(S)-Benzyloxypropyl]-6,11,11-trimethyl-1,2,3,4,5,6,-hexahydro-2,6-methano-3-benzazocin-10-ol		WO	9914199	Neuroprotective	Ischaemia, cerebral
croconazole	1H-Imidazole, 1-[1-[2-[(3-chlorophenyl)methoxy]phenyl]ethenyl]- [CAS]	77175-51-0	DE	3021467	Antifungal	Infection, fungal, general
cromoglicic acid	4H-1-Benzopyran-2-carboxylic acid, 5,5'-[(2-hydroxy-1,3-propanediyl)bis(oxy)]bis[4-oxo- [CAS]	53736-52-0			Formulation, mucosal, topical	Conjunctivitis
cromolyn	4H-1-Benzopyran-2-carboxylic acid, 5,5'-[(2-hydroxy-1,3-propanediyl)bis(oxy)]bis[4-oxo-, [CAS]	15826-37-6 16110-51-3			Formulation, inhalable, solution	Asthma
Cropropamide		633-47-6				
Crotamiton		483-63-6				
Crotethamide		61168-76-9				
Crystacide	□		US	4557935	Formulation, dermal, topical	Infection, dermatological
CS-502			EP	799823	Analgesic, other	Pain, general
CS-758	4-(1[1E,3E]-4-[trans-5-[(1R,2R)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]thio]-1,3-dioxan-2-yl]-1,3-butadienyl)-3-fluorobenzonitrile				Antifungal	Infection, fungal, general
CS-834	1-Azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid, 6-[(1'R)-1-hydroxyethyl]-4-methyl-7-oxo-3-[[(3'R)-5-oxo-3-pyrrolidinyl]thio]-, (2,2-dimethyl-1-oxopropoxy)methyl ester, [4R,5S,6S]- [CAS]	157542-49-9	EP	599512	Beta-lactam antibiotic	Infection, general

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API Generic Name	API Chemical Name	CAS No.	Patent Reference	Example of Therapeutic Use	Example of Indication
CT-052923	[(2*i*-benzo[d]1,3-dioxalan-5-methyl)amino][4-(6,7-dimethoxyquinazolin-4-yl)piperazinyl]methane-1-thione			Cardiovascular	Restenosis
CT-32228	N-(4-bromophenyl)-6-(5-chloro-2-methylphenyl)-[1,3,5]triazine-2,4-diamine			Anticancer, other	Cancer, general
Cupric Citrate		866-82-0			
Cuproxoline		13007-83-7			
CVT-2584	Ethanol, 2,2'-[[6-[[6-[[4-methoxyphenyl]methyl]amino]-9-(1-methylethyl)-9H-purin-2-yl]imino]bis- [CAS]	199986-75-9	WO 9805335	Cardiovascular	Restenosis
CX-659S	((S)-6-amino-5-(6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxamido)-3-methyl-1-phenyl-2,4-(1H,3H)-pyrimidinedione			Dermatological	Eczema, general
Cyacetacide		140-87-4			
Cyamemazine		3546-03-0			
Cyanidin		528-58-5			
CYC400			WO 00172745	Anticancer, other	Cancer, general
Cyclacillin		3485-14-1			
Cyclandelate		456-59-7			
Cyclazocine		3572-80-3			
Cyclexanone		15301-52-7			
Cyclexedrine		532-52-5			
cyclitinol	3-Cyclohexene-1-methanol, 5-hydroxy-Alpha,Alpha,4-trimethyl- [CAS]	498-71-5		COPD treatment, Respiratory	Bronchitis, chronic
cyclin D1 inhibitors			US 6033843	Anticancer, hormonal	Cancer, breast
Cyclizine		82-92-8			
Cyclobarbital		52-31-3			
Cyclobendazole		31431-43-3			

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API Generic Name	API Chemical Name	CAS No.	Patent Reference	Example of Therapeutic Use	Example of Indication
cyclobenzaprine	1-Propanamine, 3-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-N,N-dimethyl-[CAS]	303-53-7		Formulation, modified-release, other	Muscle spasm, general
Cyclobutyrol		512-16-3			
Cyclocumarol		518-20-7			
Cyclodrine		52109-93-0			
Cyclofenil		2624-43-3			
Cycloguanil		516-21-2			
Cyclomethycaine		139-62-8			
Cyclonium Iodide		6577-41-9			
Cyclopentamine		102-45-4			
Cyclopenthiazide		742-20-1			
Cyclopentobarbital		76-68-6			
Cyclopentolate		512-15-2			
cyclophosphamide	N,N-Bis(2-chloroethyl)tetrahydro-2H-1,3,2-oxazaphosphorin-2-amine-2-oxide monohydrate	50-18-0 6055-19-2		Formulation, parenteral, targeted	Cancer, general
cyclopiroxalamine	2(1H)-Pyridinone, 6-cyclohexyl-1-hydroxy-4-methyl-, cmpd with 2-aminoethanol(1:1) [CAS]	41621-49-2		Formulation, transdermal, other	Vaginitis
Cycloserine		68-41-7			
Cyclothiazide		2259-96-3			
Cyclovalone		579-23-7			
Cymarin		508-77-0			
cymserine	Carbamic acid, [4-(1-methylethyl)phenyl]-, (3aS,8aR)-1,2,3,3a,8,8a-hexahydro-1,3a,8-trimethylpyrrolo[2,3-b]indol-5-yl ester [CAS]	145200-39-8	WO 9602154	Cognition enhancer	Alzheimer's disease
Cymarin(e)		30964-13-7			
CYP2B inhibitors			US 6063606	Dermatological	Unspecified
Cyproheptadine		129-03-3			
cyproterone	(1S,2S)-6-Chloro-1,2-dihydro-17-hydroxy-3'H-cyclopropa[1,2]pregna-1,4,6-triene-3,20-dione [CAS]	2098-66-0		Radiolchemoprotective	Chemotherapy-induced injury, general

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API Generic Name	API Chemical Name	CAS No.	Patent Reference			Example of Therapeutic Use	Example of Indication
Cysteamine		60-23-1					
cystic fibrosis ther	[[4-[[3-[[4-(1-(4-hydroxyphenyl)-1-methyl-ethyl)phenoxy]methyl]phenyl]methoxy]-phenyl]iminomethyl]-, ethyl ester					Cystic fibrosis treatment	Cystic fibrosis
cytarabine	2(1H)-Pyrimidinone, 4-amino-1-[5-O-[hydroxy(octadecyloxy)phosphinyl]-β-D-arabinofuranosyl]-, [CAS]	65093-40-5 147-94-4	EP	2396015	Anticancer, antimetabolite	Anticancer, antimetabolite	Myelodysplastic syndrome
D-24851	[N-(Pyridin-4-yl)-(1-(4-chlorobenzyl)-Indol-3-yl)-glyoxyl-amide)					Anticancer, other	Cancer, general
D-4418	8-Methoxyquinoline-5-[N-(2,5-dichloropyridin-3-yl)]carboxamide					Antiasthma	Asthma
DA-8018	Benzeneacetamide, 4-(2-aminoethoxy)-N-(3-(3,4-dimethylphenyl)propyl)-3-methoxy-, monohydrochloride [CAS]	174661-97-3	US	i5242944	Analgesic, other	Analgesic, other	Pain, musculoskeletal
DA-8034			US	6025387	GI inflammatory/bowel disorders	GI inflammatory/bowel disorders	Crohn's disease
DA-7867			KR	9957803	Antibacterial, other	Antibacterial, other	Infection, general
DA-7911			KR	56034	Antiarrhythmic, other	Antiarrhythmic, other	Arthritis, rheumatoid
DA-8159	3-(1-Methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo-[4,3-d]pyrimidin-5-yl)-N-[2-(1-methylpyrrolidin-2-yl)ethyl]-4-propoxybenzenesulfonamide	KR	353014	Male sexual dysfunction	Male sexual dysfunction	Sexual dysfunction, male, general	
Dacarbazine		4342-3-4					
Daclizumab		152923-56-3					
Dactinomycin		50-76-0					
dalbavancin	5,31-Dichloro-38-de(methoxycarbonyl)-7-demethyl-19-deoxy-56-O-[2-deoxy-2-(10-methylundecanamido)-β-D-glucopyranuronosyl]-38-[N-[3-(dimethylamino)propyl]carbamoyl]-42-O-Alpha-D-mannopyranosyl-N15-methylristomycin A aglycone	171500-79-1			Peptide antibiotic	Peptide antibiotic	Infection, dermatological

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API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Dalfopristin		112362-50-2				
dalfopristin + quinupristin	Virginiamycin M1, 26-((2-(diethylamino)ethyl)sulfonyl)-26,27-dihydro-, (26R,27S)-, mixt with 4-(4-(dimethylamino)-N-methyl-L-phenylalanine)-5-(5-((1-azabicyclo(2.2.2)oct-3-ylthio)methyl)-4-oxo-L-2-piperidinecarboxylic acid) virginiamycin S1- [CAS]	126602-89-9	EP 248703	Antibiotic, other	Infection, respiratory tract, general
dalteparin	Heparin-, [CAS]	9041-08-1	US 4303651	Anticoagulant	Thromboprophylaxis
Daltroban		79094-20-5				
δ-Aminolevulinic Acid		106-60-5				
danaparoid			EP 66908	Anticoagulant	Thrombosis, venous	
danazol	Pregna-2,4-dien-20-yno[2,3-d]isoxazol-17-ol, (17Alpha)- [CAS]	17230-88-5	GB 905844	Menstruation disorders		
Danthron		117-10-2				
Dantrolene		7261-97-4				
dapiprazole	1,2,4-Triazolo[4,3-a]pyridine, 5,6,7,8-tetrahydro-3-[2-[4-(2-methylphenyl)-1-piperazinyl]ethyl]- [CAS]	72822-12-9 72822-13-0	US 4252721	Ophthalmological	Glaucoma	
dapivirine	4-[[4-[2,4,6-trimethylphenyl)amino]pyrimidin-2-yl]amino]benzonitrile	244767-67-7		Antiviral, anti-HIV	Infection, HIV/AIDS	
dapoxetine	(+)-(S)-N,N-dimethyl-Alpha-[2-(1-naphthyl-oxy)ethyl]benzylamine HCl	119356-77-3	EP 288188	Male sexual dysfunction	Premature ejaculation	
dapsone	4,4'-Sulfonyldianiline	80-08-0		Formulation, dermal, topical	Acne	
daptomycin	Daptomycin [CAS]	103060-53-3	EP 178152	Peptide antibiotic	Infection, dermatological	
Darbepoetin Alfa						
darifenacin	3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-Alpha,Alpha-diphenyl-, (S)- [CAS]	133099-04-4	EP 388054	Urological	Overactive bladder	

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daunorubicin	5,12-Naphthacenedione, 8-acetyl-10-[(3-amino-2,3,6-trideoxy-Alpha-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-, (8S-cis)- [CAS]	20830-81-3	US	5441745	Formulation, optimized, liposomes	Cancer, sarcoma, Kaposi's
DAX, SciClone	3-diallyl-8-cyclohexylxanthine				Cystic fibrosis treatment	Cystic fibrosis
DB-67	7-tert-Butyldimethylsilyl-10-hydroxycamptothecin	18530-30-8			Anticancer, other	Cancer, general
d-Camphocarboxylic Acid						
DCF-987	Dextran		US	5514665	Formulation, other	Cystic fibrosis
DDT		50-29-3				
Deaminooxytocin		113-78-0				
Deanol		108-01-0				
Debrisoquin		1131-64-2				
Decamethonium		541-22-0				
Decimemide		14817-09-5				
decitabine	1,3,5-Triazin-2(1H)-one, 4-amino-1-(2-deoxy-4-O-sulfo-pentofuranosyl)-[CAS]	2338-46-0 2353-33-5			Anticancer, antimetabolite	Myelodysplastic syndrome
declopramide	Benzamide, 4-amino-3-chloro-N-(2-(diethylamino)ethyl)- [CAS]	891-60-1	WO	9732582	Anticancer, other	Cancer, colorectal
Deferiprone		30652-11-0				
Deferoxamine		70-51-9				
deflazacort	5?H-Pregna-1,4-diene[17,16-d]oxazole-3,20-dione, 21-(acetyloxy)-11-hydroxy-2-methyl-, (11b,16a)- [CAS]	14484-47-0 74712-58-8	GB	1077393	Hormone	Asthma
Defosfamide		3733-81-1				

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degarelix	N-acetyl-3-(naphtalen-2-yl)-D-alanyl-4-chloro-D-phenylalanyl-3-(pyridin-3-yl)-D-alanyl-L-seryl-4-[[[(4S)-2,6-dioxohexahydropyrimidin-4-yl](carbamoyl)amino]-L-phenylalanyl-4-(carbamoylamino)-D-phenylalanyl-L-leucyl-N6-(1-methylethyl)-L-lysyl-L-prolyl-D-alaninamide	214766-78-6		Anticancer, hormonal	Cancer, prostate
dehydroascorbic acid	L-threo-2,3-Hexodiulosonic acid gamma-lactone	490-83-5		Cognition enhancer	Alzheimer's disease
Dehydrocholic Acid		81-23-2			
Dehydroemetine		4914-30-1			
delapril	Glycine, N-[2,3-dihydro-1H-inden-2-yl)-N-[N-[1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-, (S)- [CAS]	83435-66-9 83435-67-0	EP 51391	Antihypertensive, renin system	Hypertension, general
delapril+manidipine	Glycine, N-(2,3-dihydro-1H-inden-2-yl)-N-[N-[1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-, (S)-3,5-Pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-, 2-[4-(diphenylmethyl)-1-piperazinyl]ethyl methyl ester [CAS]		FR 2733911	Formulation, fixed-dose combinations	Hypertension, general
delavirdine	Piperazine, 1-[3-[(1-methylethyl)amino]-2-pyridinyl]-4-[[5-(methylsulfonyl)amino]-1H-indol-2-yl]carbonyl]- [CAS]	136817-59-9	WO 9109849	Antiviral, anti-HIV	Infection, HIV/AIDS
Delmadinone		13698-49-2			
Delmopinol		79874-76-3			
delorazepam	2H-1,4-Benzodiazepin-2-one, 7-chloro-5-(2-chlorophenyl)-1,3-dihydro- [CAS]	2894-67-9	CH 498029	Anxiolytic	
delucemine	3,3-Bis-(m-fluorophenyl)-N-methylpropylamine [CAS]	186495-99-8		Neuroprotective	Ischaemia, cerebral
Demanyl		69069-62-2			
Demecarium		56-94-0			

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API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
demeclocycline	2-Naphthacenecarboxamide, 7-chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-1,11-dioxo-, [4S-(4Alpha,4aAlpha,5aAlpha,6ß,12aAlpha)]- [CAS]	127-33-3			Formulation, modified-release, <=24hr	Infection, general
Demecolcine		477-30-5				
Demegestone		10116-22-0				
Demexiptiline		24701-51-7				
denaverine	Benzeneacetic acid, Alpha-(2-ethylbutoxy)-Alpha-phenyl-, 2-(dimethylamino)ethyl ester, [CAS]	3321-06-0	DE	4133785	Analgesic, NSAID	Pain, musculoskeletal
Denileukin Diftitox		1731146-27-5				
Denopamine		71771-90-9				
Denopterin		22006-84-4				
Deoxycholic Acid		83-44-3				
Deoxycorticosterone		64-85-7				
Deoxydihydrostreptomycin		56-47-3				
		26086-49-7				
Deoxyepinephrine		501-15-5				
Depreotide		161982-62-3				
dapsinepeptide	L-Valine, N-[(3S,4E)-3-hydroxy-7-mercapto-1-oxo-4-heptenyl]-D-valyl-D-cysteinyl-(2Z)-2-amino-2-butenoyl-, (4-1)-lactone, cyclic (1-2)-disulfide [CAS]	128517-07-7	EP	352646	Anticancer, antibiotic	Cancer, general
Deptropine		604-51-3				
Dequalinium		522-51-0				
dersalazine	Benzoic acid, 2-hydroxy-5-[[4-[3-H-[2-methyl-1H-imidazo[4,5-c]pyridin-1-yl]methyl]-1-piperidinyl]-3-oxo-1-phenyl-1-propenyl]phenyl]azo] (Z) [CAS]	188913-57-7 188913-58-8	US	5747477	Anti-inflammatory	Colitis, ulcerative
Deserpidine		131-01-1				

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API Generic Name	API Chemical Name	CAS No.	Patent Reference	Example of Therapeutic Use	Example of Indication
desferrioxamine	Butanediamide, N'-[5-[[4-[[5-(acetylhydroxyamino)pentyl]amino]-1,4-dioxobutyl]hydroxyamino]pentyl]-N-[5-aminopentyl]-N-hydroxy- [CAS]	70-51-9		Antidote	Poisoning, metal
Desflurane		57041-67-5			
Desipramine		50-47-5			
Deslanoside		17598-65-1			
desloratadine	5H-Benzo[5,6]cyclohepta[1,2-b]pyridine, 8-chloro-6,11-dihydro-11-(4-piperidinylidene)- [CAS]	100643-71-8	US 5595997	Antiallergic, non-asthma	Rhinitis, allergic, perennial
deslorelin	Luteinizing hormone-releasing factor (pig), 6-D-tryptophan-9-(N-ethyl-L-prolinamide)-10-deglycinamide- [CAS]	57773-65-6	US 4034082	Releasing hormones	Cancer, prostate
desmopressin	Vasopressin, 1-(3-mercaptopropanoic acid)-8-D-arginine- [CAS]	16679-58-6	DE 2948345	Hormone	Enuresis
Desogestrel		54024-22-5			
desogestrel + estradiol	Estra-1,3,5(10)-triene-3,17-diol (17ß)-, mixt. with (17Alpha)-13-ethyl-11-methylene-18,19-dinorpregn-4-en-20-yn-17-ol [CAS]	122364-17-4		Menopausal disorders	Hormone replacement therapy
desogestrel, Akzo Nobel	18,19-Dinorpregn-4-en-20-yn-17-ol, 13-ethyl-11-methylene-, (17Alpha)- [CAS]	54024-55-5		Formulation, oral, other	Contraceptive, female
desogestrel+ethinylestradi (1)	18,19-Dinorpregn-4-en-20-yn-17-ol, 13-ethyl-11-methylene-, (17Alpha)- [CAS]	54024-22-5 71138-35-7	US 3927046	Formulation, oral, other	Contraceptive, female
Desomorphine		427-00-9			
Desonide		638-94-8			
Desoximetasone		382-67-2			
Detaxtran		9015-73-0			
Devacade			WO 9308176	Analgesic, other	Pain, general
dexamethasone	Pregna-1,4-diene-3,20-dione,9-fluoro-11,17,21-trihydroxy-16-methyl-, (11ß,16Alpha)- [CAS]	50-02-2 2392-39-4 312-93-6		Formulation, other	Inflammation, ocular
dexanabinol	6H-Dibenzo[b,d]pyran-9-methanol, 3-(1,1-dimethylheptyl)-hexahydro-1-hydroxy-6,6-dimethyl-, (6aS-trans)- [CAS]	112924-45-5	EP 427518	Neuroprotective	Head trauma

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dexecadotril	Glycine, N-[2-[(acetylthio)methyl]-1-oxo-3-phenylpropyl]-, phenylmethyl ester, (R)- [CAS]	112573-72-5	EP	318377	Alimentary/Metabolic, other	Unspecified
dexefaroxan	1H-Imidazole, 2-(2-ethyl-2,3-dihydro-2-benzofuranyl)-4,5-dihydro- [CAS]	89197-00-2 89197-32-0	EP	71368	Cognition enhancer	Alzheimer's disease
Dexetimide		21888-98-2				
dexibuprofen	Benzeneacetic acid, Alpha-methyl-4-(2-methylpropyl)-, (AlphaS)- [CAS]	51146-56-6			Analgesic, NSAID	Pain, general
dexketoprofen	Benzeneacetic acid, 3-benzoyl-Alpha-methyl-, (S)- [CAS]	22161-81-5			Anti-inflammatory	Inflammation, general
dexloxiglumide	Pentanoic acid, 4-[(3,4-dichlorobenzoyl)amino]-5-[(3-methoxypropyl)pentylamino]-5-oxo-, (R)- [CAS]	119817-90-2	EP	0344184	GI inflammatory/bowel disorders	Irritable bowel syndrome
dexmedetomidine	1H-Imidazole, 4-[1-(2,3-dimethylphenyl)ethyl]-, (R)- [CAS]	113775-47-6 86347-15-1	EP	187471	Hypnotic/Sedative	Anaesthesia
dexmethylphenidate	2-Piperidineacetic acid, Alpha-phenyl-, methyl ester, (AlphaR,2R)-	19262-68-1			Psychostimulant	Attention deficit disorder
Dexpanthenol		81-13-0				
dexrazoxane	2,6-Piperazinedione, 4,4'-(1-methyl-1,2-ethanediyl)bis-, (S)- [CAS]	24584-09-6	DE	1910283	Radio/chemoprotective	Chemotherapy-induced injury, general
Dextran-1	Dextran [CAS]	9004-54-0			Plasma substitute	
Dextranomer		56087-11-7				
Dextroamphetamine		51-64-9				
dextromethorphan	Morphinan, 3-methoxy-17-methyl-, (9Alpha,13Alpha,14Alpha)-,	6700-34-1 125-71-3	US	4221788	Formulation, oral, other	Cough, Emotional lability
Dextromoramide		357-56-2				
dextropropoxyphene	Benzeneethanol, Alpha-[2-(dimethylamino)-1-methylethyl]-Alpha-phenyl-, propanoate (ester), [S-(R*,S*)]- [CAS]	469-62-5			Formulation, modified-release, other	Pain, general
Dezocine		53648-55-8				
DF-1012	N-Tropyl 7-azaindol-3-ylcarboxamide	163220-65-3	WO	9504742	Respiratory	Respiratory disease, general
DFA-IV	di-D-fructofuranose 2,6':6,2' dianhydride		US	5700832	Antianaemic	Anaemia, aplastic

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API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
d-Fenchone		4695-62-9				
D-Glucuronolactone		32449-92-6				
Diab II	Diab II	309956-85-2	US	6153632	Antidiabetic	Diabetes, Type II
diacerein	2-Anthracenecarboxylic acid, 4,5-bis(acetyloxy)-9,10-dihydro-9,10-dioxo- [CAS]	13739-02-1	US	4244966	Antiarthritic, other	Arthritis, rheumatoid
Diampromide		552-25-0				
Diamthazole		136-96-9				
Diathymosulfone		5964-62-5				
Diatrizoate		737-31-5				
diazepam	2H-1,4-Benzodiazepin-2-one, 7-chloro-1,3-dihydro-1-methyl-5-phenyl- [CAS]	439-14-5			Formulation, transmucosal, systemic	Anxiety, epilepsy, general
Diaziquone		57998-68-2				
Diazoxide		364-98-7				
dibekacin	D-Streptamine, O-3-amino-3-deoxy-Alpha-D-glucopyranosyl-(1-6)-O-[2,6-diamino-2,3,4,6-tetradeoxy-Alpha-D-erythro-hexopyranosyl-(1-4)]-2-deoxy-, sulfate (salt)[CAS]	34493-98-6 58580-55-5	GB	1349302	Aminoglycoside antibiotic	Infection, general
Dibenzepin		4498-32-2				
Dibromopropamidine		496-00-4				
Dibucaine		61-12-1				
Dichloralphenazone		480-30-8				
Dichloramine T		473-34-7				
Dichlorisone		7008-26-6				
Dichlorobenzyl Alcohol		1777-82-8				
Dichlorophen		97-23-4				
Dichlorophenarsine		536-29-8				
Dichlorphenamide		120-97-8				
diclofenac + HA	Hyaluronic acid + benzeneacetic acid, 2-[(2,6-dichlorophenyl)amino]- [CAS]				Formulation, transdermal, systemic	Keratosis
diclofenac	Benzeneacetic acid, 2-[(2,6-dichlorophenyl)amino]-, [CAS]	15307-79-6 15307-86-5 15307-81-0			Formulation, modified-release, <=24hr	Pain, general